

# 5

## Cancer

ARTHUR SCHATZKIN, D. YVONNE JONES,  
TAMARA B. HARRIS, PHILIP R. TAYLOR,  
ROBERT N. HOOVER, CHRISTINE L. CARTER,  
REGINA G. ZIEGLER, AND LOUISE A. BRINTON

### EPIDEMIOLOGIC INVESTIGATIONS OF CANCER IN NHEFS

At least three features make the data set from the NHANES I (National Health and Nutrition Examination Survey-I) Epidemiologic Follow-up Study, or NHEFS, particularly useful for researchers in cancer epidemiology. First, since the study was based on a probability sample of the population of the United States, the NHEFS cohort has greater heterogeneity in educational background, occupation, and geographic residence than one traditionally finds in cohorts. Second, information on characteristics and exposures of subjects was gathered before diagnosis. Cancer is known to affect many systems within the body and may certainly affect constituents of the blood and other biologic end points, as well as various aspects of life-style, including diet and exercise. Moreover, the diagnosis of cancer may influence a person's recall and reporting of information. These potential problems of reverse causation and recall bias are obviated in large part by the prospective cohort design of NHEFS. Third, relatively "hard" data on cancer end points are available from both hospital records and death certificates.

We have previously used the NHEFS data set to examine three hypotheses of considerable public health importance: (1) Alcohol consumption is positively associated with breast cancer; (2) dietary fat consumption is positively associated with breast cancer; and (3) serum cholesterol is inversely associated with cancer (at all sites combined and at certain specific sites, especially the colorectum). In this chapter we present a review of our earlier analyses (Jones et al. 1987; Schatzkin, Jones et al. 1987; Schatzkin, Taylor et al. 1987; Schatzkin et al. 1988). In addition, we present results of a study of the relation between socioeconomic status and cancer. These studies reflect a common premise that the identification of socioenvironmental factors involved in the etiology of cancer is a critical step in the prevention of malignant disease.

## IDENTIFICATION OF CASES: GENERAL CONSIDERATIONS

For our analyses involving the incidence of "all cancers," a study participant was classified as an incident case if there was any diagnosis of cancer (International Classification of Diseases codes 140 through 208, excluding nonmelanoma skin cancer, ICD code 173) on a hospital record or death certificate. (With incident cases identified from death certificates, both the underlying and contributing causes of death were relevant.) Cancer cases at specific sites were similarly identified from the hospital records and/or death certificates. A few cases listed as primary lung cancer were found on review of the hospital records to be secondary cancers (metastatic from some other site). An individual could have had an incident cancer at more than one site.

For cases identified through hospital records, the date of first admission for a specific cancer listed in the discharge diagnosis was regarded as the date of incidence for that site. The date of death was considered to be the incidence date for cancers for which the only data available were those on the death certificate.

In analyses of mortality, only cancer listed as the underlying cause of death was considered to be a case.

We excluded persons with prevalent cancer at baseline from all our analyses. A person was considered to be a prevalent case if, at the first hospitalization, one of the ICD V-codes indicating a "history" of cancer at a specific site was listed. A person with a history of cancer at one site, however, was still at risk for cancer at another site and would not have been excluded from some of the site-specific investigations.

## ALCOHOL AND BREAST CANCER

Evidence that alcohol consumption increases the risk of breast cancer in women appeared over a decade ago (Williams and Horm 1977). Since that time, a number of epidemiologic studies have shown this association. Although not all case-control investigations of the relation between alcohol consumption and breast cancer showed the positive association (Begg et al. 1983; Byers and Funch 1982; Paganini-Hill and Ross 1983; Webster et al. 1983; Wynder et al. 1960), the majority of them indicated that the risk of breast cancer increased with moderate alcohol consumption (Harvey et al. 1987; La Vecchia et al. 1985; Le et al. 1984; O'Connell et al. 1987; Rosenberg et al. 1982; Talamini et al. 1984). Three cohort studies observed an elevation in risk of 50–100% in relation to drinking. Hiatt and Bawol reported a 40% excess risk among women consuming three or more drinks per day (Hiatt and Bawol 1984). Willet et al. showed a 60% increase in risk for women drinking a little more than a drink per day, with a dose-response relation being evident (Willet et al. 1987). Hiatt et al. recently showed that women consuming one or two drinks per day had a 50% elevation in risk, with "past drinkers" being at more than twice the risk of nondrinkers (Hiatt et al. 1988).

## Analytic Methodology

The original NHEFS cohort included 10,000 women. We initially identified 10,000 records and 20 from de

In this study (Schauman et al. 1988), the cohort as follows: 30 women were missing; 281 women were excluded from the NHANES I interview who had been affected by these cancers. 483 women were found because they refused to be interviewed. 121 women were considered to be prevalent cases of cancer more than one of these.

After these exclusions, the cohort was 10 years.

We were concerned that the cohort was roughly comparable to the age- and race-specific incidence rates in our cohort. The ratio of the incidence rates, 0.89–1.28).

Questions on frequency of drinking were asked at the baseline interview. The questions were: "How often do you drink beer, wine, or liquor during the past 12 months?" and "How often do you drink beer, wine, or liquor during the past 12 months?" The possible answers were: "less than 12 times per year," "12 to 24 times per year," "25 to 36 times per year," "37 to 48 times per year," "49 to 60 times per year," "61 to 72 times per year," "73 to 84 times per year," "85 to 96 times per year," "97 to 108 times per year," "109 to 120 times per year," "121 to 132 times per year," "133 to 144 times per year," "145 to 156 times per year," "157 to 168 times per year," "169 to 180 times per year," "181 to 192 times per year," "193 to 204 times per year," "205 to 216 times per year," "217 to 228 times per year," "229 to 240 times per year," "241 to 252 times per year," "253 to 264 times per year," "265 to 276 times per year," "277 to 288 times per year," "289 to 300 times per year," "301 to 312 times per year," "313 to 324 times per year," "325 to 336 times per year," "337 to 348 times per year," "349 to 360 times per year," "361 to 372 times per year," "373 to 384 times per year," "385 to 396 times per year," "397 to 408 times per year," "409 to 420 times per year," "421 to 432 times per year," "433 to 444 times per year," "445 to 456 times per year," "457 to 468 times per year," "469 to 480 times per year," "481 to 492 times per year," "493 to 504 times per year," "505 to 516 times per year," "517 to 528 times per year," "529 to 540 times per year," "541 to 552 times per year," "553 to 564 times per year," "565 to 576 times per year," "577 to 588 times per year," "589 to 600 times per year," "601 to 612 times per year," "613 to 624 times per year," "625 to 636 times per year," "637 to 648 times per year," "649 to 660 times per year," "661 to 672 times per year," "673 to 684 times per year," "685 to 696 times per year," "697 to 708 times per year," "709 to 720 times per year," "721 to 732 times per year," "733 to 744 times per year," "745 to 756 times per year," "757 to 768 times per year," "769 to 780 times per year," "781 to 792 times per year," "793 to 804 times per year," "805 to 816 times per year," "817 to 828 times per year," "829 to 840 times per year," "841 to 852 times per year," "853 to 864 times per year," "865 to 876 times per year," "877 to 888 times per year," "889 to 900 times per year," "901 to 912 times per year," "913 to 924 times per year," "925 to 936 times per year," "937 to 948 times per year," "949 to 960 times per year," "961 to 972 times per year," "973 to 984 times per year," "985 to 996 times per year," "997 to 1008 times per year," "1009 to 1020 times per year," "1021 to 1032 times per year," "1033 to 1044 times per year," "1045 to 1056 times per year," "1057 to 1068 times per year," "1069 to 1080 times per year," "1081 to 1092 times per year," "1093 to 1104 times per year," "1105 to 1116 times per year," "1117 to 1128 times per year," "1129 to 1140 times per year," "1141 to 1152 times per year," "1153 to 1164 times per year," "1165 to 1176 times per year," "1177 to 1188 times per year," "1189 to 1200 times per year," "1201 to 1212 times per year," "1213 to 1224 times per year," "1225 to 1236 times per year," "1237 to 1248 times per year," "1249 to 1260 times per year," "1261 to 1272 times per year," "1273 to 1284 times per year," "1285 to 1296 times per year," "1297 to 1308 times per year," "1309 to 1320 times per year," "1321 to 1332 times per year," "1333 to 1344 times per year," "1345 to 1356 times per year," "1357 to 1368 times per year," "1369 to 1380 times per year," "1381 to 1392 times per year," "1393 to 1404 times per year," "1405 to 1416 times per year," "1417 to 1428 times per year," "1429 to 1440 times per year," "1441 to 1452 times per year," "1453 to 1464 times per year," "1465 to 1476 times per year," "1477 to 1488 times per year," "1489 to 1500 times per year," "1501 to 1512 times per year," "1513 to 1524 times per year," "1525 to 1536 times per year," "1537 to 1548 times per year," "1549 to 1560 times per year," "1561 to 1572 times per year," "1573 to 1584 times per year," "1585 to 1596 times per year," "1597 to 1608 times per year," "1609 to 1620 times per year," "1621 to 1632 times per year," "1633 to 1644 times per year," "1645 to 1656 times per year," "1657 to 1668 times per year," "1669 to 1680 times per year," "1681 to 1692 times per year," "1693 to 1704 times per year," "1705 to 1716 times per year," "1717 to 1728 times per year," "1729 to 1740 times per year," "1741 to 1752 times per year," "1753 to 1764 times per year," "1765 to 1776 times per year," "1777 to 1788 times per year," "1789 to 1800 times per year," "1801 to 1812 times per year," "1813 to 1824 times per year," "1825 to 1836 times per year," "1837 to 1848 times per year," "1849 to 1860 times per year," "1861 to 1872 times per year," "1873 to 1884 times per year," "1885 to 1896 times per year," "1897 to 1908 times per year," "1909 to 1920 times per year," "1921 to 1932 times per year," "1933 to 1944 times per year," "1945 to 1956 times per year," "1957 to 1968 times per year," "1969 to 1980 times per year," "1981 to 1992 times per year," "1993 to 2004 times per year," "2005 to 2016 times per year," "2017 to 2028 times per year," "2029 to 2040 times per year," "2041 to 2052 times per year," "2053 to 2064 times per year," "2065 to 2076 times per year," "2077 to 2088 times per year," "2089 to 2100 times per year," "2101 to 2112 times per year," "2113 to 2124 times per year," "2125 to 2136 times per year," "2137 to 2148 times per year," "2149 to 2160 times per year," "2161 to 2172 times per year," "2173 to 2184 times per year," "2185 to 2196 times per year," "2197 to 2208 times per year," "2209 to 2220 times per year," "2221 to 2232 times per year," "2233 to 2244 times per year," "2245 to 2256 times per year," "2257 to 2268 times per year," "2269 to 2280 times per year," "2281 to 2292 times per year," "2293 to 2304 times per year," "2305 to 2316 times per year," "2317 to 2328 times per year," "2329 to 2340 times per year," "2341 to 2352 times per year," "2353 to 2364 times per year," "2365 to 2376 times per year," "2377 to 2388 times per year," "2389 to 2400 times per year," "2401 to 2412 times per year," "2413 to 2424 times per year," "2425 to 2436 times per year," "2437 to 2448 times per year," "2449 to 2460 times per year," "2461 to 2472 times per year," "2473 to 2484 times per year," "2485 to 2496 times per year," "2497 to 2508 times per year," "2509 to 2520 times per year," "2521 to 2532 times per year," "2533 to 2544 times per year," "2545 to 2556 times per year," "2557 to 2568 times per year," "2569 to 2580 times per year," "2581 to 2592 times per year," "2593 to 2604 times per year," "2605 to 2616 times per year," "2617 to 2628 times per year," "2629 to 2640 times per year," "2641 to 2652 times per year," "2653 to 2664 times per year," "2665 to 2676 times per year," "2677 to 2688 times per year," "2689 to 2700 times per year," "2701 to 2712 times per year," "2713 to 2724 times per year," "2725 to 2736 times per year," "2737 to 2748 times per year," "2749 to 2760 times per year," "2761 to 2772 times per year," "2773 to 2784 times per year," "2785 to 2796 times per year," "2797 to 2808 times per year," "2809 to 2820 times per year," "2821 to 2832 times per year," "2833 to 2844 times per year," "2845 to 2856 times per year," "2857 to 2868 times per year," "2869 to 2880 times per year," "2881 to 2892 times per year," "2893 to 2904 times per year," "2905 to 2916 times per year," "2917 to 2928 times per year," "2929 to 2940 times per year," "2941 to 2952 times per year," "2953 to 2964 times per year," "2965 to 2976 times per year," "2977 to 2988 times per year," "2989 to 3000 times per year," "3001 to 3012 times per year," "3013 to 3024 times per year," "3025 to 3036 times per year," "3037 to 3048 times per year," "3049 to 3060 times per year," "3061 to 3072 times per year," "3073 to 3084 times per year," "3085 to 3096 times per year," "3097 to 3108 times per year," "3109 to 3120 times per year," "3121 to 3132 times per year," "3133 to 3144 times per year," "3145 to 3156 times per year," "3157 to 3168 times per year," "3169 to 3180 times per year," "3181 to 3192 times per year," "3193 to 3204 times per year," "3205 to 3216 times per year," "3217 to 3228 times per year," "3229 to 3240 times per year," "3241 to 3252 times per year," "3253 to 3264 times per year," "3265 to 3276 times per year," "3277 to 3288 times per year," "3289 to 3300 times per year," "3301 to 3312 times per year," "3313 to 3324 times per year," "3325 to 3336 times per year," "3337 to 3348 times per year," "3349 to 3360 times per year," "3361 to 3372 times per year," "3373 to 3384 times per year," "3385 to 3396 times per year," "3397 to 3408 times per year," "3409 to 3420 times per year," "3421 to 3432 times per year," "3433 to 3444 times per year," "3445 to 3456 times per year," "3457 to 3468 times per year," "3469 to 3480 times per year," "3481 to 3492 times per year," "3493 to 3504 times per year," "3505 to 3516 times per year," "3517 to 3528 times per year," "3529 to 3540 times per year," "3541 to 3552 times per year," "3553 to 3564 times per year," "3565 to 3576 times per year," "3577 to 3588 times per year," "3589 to 3600 times per year," "3601 to 3612 times per year," "3613 to 3624 times per year," "3625 to 3636 times per year," "3637 to 3648 times per year," "3649 to 3660 times per year," "3661 to 3672 times per year," "3673 to 3684 times per year," "3685 to 3696 times per year," "3697 to 3708 times per year," "3709 to 3720 times per year," "3721 to 3732 times per year," "3733 to 3744 times per year," "3745 to 3756 times per year," "3757 to 3768 times per year," "3769 to 3780 times per year," "3781 to 3792 times per year," "3793 to 3804 times per year," "3805 to 3816 times per year," "3817 to 3828 times per year," "3829 to 3840 times per year," "3841 to 3852 times per year," "3853 to 3864 times per year," "3865 to 3876 times per year," "3877 to 3888 times per year," "3889 to 3900 times per year," "3901 to 3912 times per year," "3913 to 3924 times per year," "3925 to 3936 times per year," "3937 to 3948 times per year," "3949 to 3960 times per year," "3961 to 3972 times per year," "3973 to 3984 times per year," "3985 to 3996 times per year," "3997 to 4008 times per year," "4009 to 4020 times per year," "4021 to 4032 times per year," "4033 to 4044 times per year," "4045 to 4056 times per year," "4057 to 4068 times per year," "4069 to 4080 times per year," "4081 to 4092 times per year," "4093 to 4104 times per year," "4105 to 4116 times per year," "4117 to 4128 times per year," "4129 to 4140 times per year," "4141 to 4152 times per year," "4153 to 4164 times per year," "4165 to 4176 times per year," "4177 to 4188 times per year," "4189 to 4200 times per year," "4201 to 4212 times per year," "4213 to 4224 times per year," "4225 to 4236 times per year," "4237 to 4248 times per year," "4249 to 4260 times per year," "4261 to 4272 times per year," "4273 to 4284 times per year," "4285 to 4296 times per year," "4297 to 4308 times per year," "4309 to 4320 times per year," "4321 to 4332 times per year," "4333 to 4344 times per year," "4345 to 4356 times per year," "4357 to 4368 times per year," "4369 to 4380 times per year," "4381 to 4392 times per year," "4393 to 4404 times per year," "4405 to 4416 times per year," "4417 to 4428 times per year," "4429 to 4440 times per year," "4441 to 4452 times per year," "4453 to 4464 times per year," "4465 to 4476 times per year," "4477 to 4488 times per year," "4489 to 4500 times per year," "4501 to 4512 times per year," "4513 to 4524 times per year," "4525 to 4536 times per year," "4537 to 4548 times per year," "4549 to 4560 times per year," "4561 to 4572 times per year," "4573 to 4584 times per year," "4585 to 4596 times per year," "4597 to 4608 times per year," "4609 to 4620 times per year," "4621 to 4632 times per year," "4633 to 4644 times per year," "4645 to 4656 times per year," "4657 to 4668 times per year," "4669 to 4680 times per year," "4681 to 4692 times per year," "4693 to 4704 times per year," "4705 to 4716 times per year," "4717 to 4728 times per year," "4729 to 4740 times per year," "4741 to 4752 times per year," "4753 to 4764 times per year," "4765 to 4776 times per year," "4777 to 4788 times per year," "4789 to 4800 times per year," "4801 to 4812 times per year," "4813 to 4824 times per year," "4825 to 4836 times per year," "4837 to 4848 times per year," "4849 to 4860 times per year," "4861 to 4872 times per year," "4873 to 4884 times per year," "4885 to 4896 times per year," "4897 to 4908 times per year," "4909 to 4920 times per year," "4921 to 4932 times per year," "4933 to 4944 times per year," "4945 to 4956 times per year," "4957 to 4968 times per year," "4969 to 4980 times per year," "4981 to 4992 times per year," "4993 to 5004 times per year," "5005 to 5016 times per year," "5017 to 5028 times per year," "5029 to 5040 times per year," "5041 to 5052 times per year," "5053 to 5064 times per year," "5065 to 5076 times per year," "5077 to 5088 times per year," "5089 to 5100 times per year," "5101 to 5112 times per year," "5113 to 5124 times per year," "5125 to 5136 times per year," "5137 to 5148 times per year," "5149 to 5160 times per year," "5161 to 5172 times per year," "5173 to 5184 times per year," "5185 to 5196 times per year," "5197 to 5208 times per year," "5209 to 5220 times per year," "5221 to 5232 times per year," "5233 to 5244 times per year," "5245 to 5256 times per year," "5257 to 5268 times per year," "5269 to 5280 times per year," "5281 to 5292 times per year," "5293 to 5304 times per year," "5305 to 5316 times per year," "5317 to 5328 times per year," "5329 to 5340 times per year," "5341 to 5352 times per year," "5353 to 5364 times per year," "5365 to 5376 times per year," "5377 to 5388 times per year," "5389 to 5400 times per year," "5401 to 5412 times per year," "5413 to 5424 times per year," "5425 to 5436 times per year," "5437 to 5448 times per year," "5449 to 5460 times per year," "5461 to 5472 times per year," "5473 to 5484 times per year," "5485 to 5496 times per year," "5497 to 5508 times per year," "5509 to 5520 times per year," "5521 to 5532 times per year," "5533 to 5544 times per year," "5545 to 5556 times per year," "5557 to 5568 times per year," "5569 to 5580 times per year," "5581 to 5592 times per year," "5593 to 5604 times per year," "5605 to 5616 times per year," "5617 to 5628 times per year," "5629 to 5640 times per year," "5641 to 5652 times per year," "5653 to 5664 times per year," "5665 to 5676 times per year," "5677 to 5688 times per year," "5689 to 5700 times per year," "5701 to 5712 times per year," "5713 to 5724 times per year," "5725 to 5736 times per year," "5737 to 5748 times per year," "5749 to 5760 times per year," "5761 to 5772 times per year," "5773 to 5784 times per year," "5785 to 5796 times per year," "5797 to 5808 times per year," "5809 to 5820 times per year," "5821 to 5832 times per year," "5833 to 5844 times per year," "5845 to 5856 times per year," "5857 to 5868 times per year," "5869 to 5880 times per year," "5881 to 5892 times per year," "5893 to 5904 times per year," "5905 to 5916 times per year," "5917 to 5928 times per year," "5929 to 5940 times per year," "5941 to 5952 times per year," "5953 to 5964 times per year," "5965 to 5976 times per year," "5977 to 5988 times per year," "5989 to 6000 times per year," "6001 to 6012 times per year," "6013 to 6024 times per year," "6025 to 6036 times per year," "6037 to 6048 times per year," "6049 to 6060 times per year," "6061 to 6072 times per year," "6073 to 6084 times per year," "6085 to 6096 times per year," "6097 to 6108 times per year," "6109 to 6120 times per year," "6121 to 6132 times per year," "6133 to 6144 times per year," "6145 to 6156 times per year," "6157 to 6168 times per year," "6169 to 6180 times per year," "6181 to 6192 times per year," "6193 to 6204 times per year," "6205 to 6216 times per year," "6217 to 6228 times per year," "6229 to 6240 times per year," "6241 to 6252 times per year," "6253 to 6264 times per year," "6265 to 6276 times per year," "6277 to 6288 times per year," "6289 to 6300 times per year," "6301 to 6312 times per year," "6313 to 6324 times per year," "6325 to 6336 times per year," "6337 to 6348 times per year," "6349 to 6360 times per year," "6361 to 6372 times per year," "6373 to 6384 times per year," "6385 to 6396 times per year," "6397 to 6408 times per year," "6409 to 6420 times per year," "6421 to 6432 times per year," "6433 to 6444 times per year," "6445 to 6456 times per year," "6457 to 6468 times per year," "6469 to 6480 times per year," "6481 to 6492 times per year," "6493 to 6504 times per year," "6505 to 6516 times per year," "6517 to 6528 times per year," "6529 to 6540 times per year," "6541 to 6552 times per year," "6553 to 6564 times per year," "6565 to 6576 times per year," "6577 to 6588 times per year," "6589 to 6600 times per year," "6601 to 6612 times per year," "6613 to 6624 times per year," "6625 to 6636 times per year," "6637 to 6648 times per year," "6649 to 6660 times per year," "6661 to 6672 times per year," "6673 to 6684 times per year," "6685 to 6696 times per year," "6697 to 6708 times per year," "6709 to 6720 times per year," "6721 to 6732 times per year," "6733 to 6744 times per year," "6745 to 6756 times per year," "6757 to 6768 times per year," "6769 to 6780 times per year," "6781 to 6792 times per year," "6793 to 6804 times per year," "6805 to 6816 times per year," "6817 to 6828 times per year," "6829 to 6840 times per year," "6841 to 6852 times per year," "6853 to 6864 times per year," "6865 to 6876 times per year," "6877 to 6888 times per year," "6889 to 6900 times per year," "6901 to 6912 times per year," "6913 to 6924 times per year," "6925 to 6936 times per year," "6937 to 6948 times per year," "6949 to 6960 times per year," "6961 to 6972 times per year," "6973 to 6984 times per year," "6985 to 6996 times per year," "6997 to 7008 times per year," "7009 to 7020 times per year," "7021 to 7032 times per year," "7033 to 7044 times per year," "7045 to 7056 times per year," "7057 to 7068 times per year," "7069 to 7080 times per year," "7081 to 7092 times per year," "7093 to 7104 times per year," "7105 to 7116 times per year," "7117 to 7128 times per year," "7129 to 7140 times per year," "7141 to 7152 times per year," "7153 to 7164 times per year," "7165 to 7176 times per year," "7177 to 7188 times per year," "7189 to 7200 times per year," "7201 to 7212 times per year," "7213 to 7224 times per year," "7225 to 7236 times per year," "7237 to 7248 times per year," "7249 to 7260 times per year," "7261 to 7272 times per year," "7273 to 7284 times per year," "7285 to 7296 times per year," "7297 to 7308 times per year," "7309 to 7320 times per year," "7321 to 7332 times per year," "7333 to 7344 times per year," "7345 to 7356 times per year," "7357 to 7368 times per year," "7369 to 7380 times per year," "7381 to 7392 times per year," "7393 to 7404 times per year," "7405 to 7416 times per year," "7417 to 7428 times per year," "7429 to 7440 times per year," "7441 to 7452 times per year," "7453 to 7464 times per year," "7465 to 7476 times per year," "7477 to 7488 times per year," "7489 to 7500 times per year," "7501 to 7512 times per year," "7513 to 7524 times per year," "7525 to 7536 times per year," "7537 to 7548 times per year," "7549 to 7560 times per year," "7561 to 7572 times per year," "7573 to 7584 times per year," "7585 to 7596 times per year," "7597 to 7608 times per year," "7609 to 7620 times per year," "7621 to 7632 times per year," "7633 to 7644 times per year," "7645 to 7656 times per year," "7657 to 7668 times per year," "7669 to 7680 times per year," "7681 to 7692 times per year," "7693 to 7704 times per year," "7705 to 7716 times per year," "7717 to 7728 times per year," "7729 to 7740 times per year," "7741 to 7752 times per year," "7753 to 7764 times per year," "7765 to 7776 times per year," "7777 to 7788 times per year," "7789 to 7800 times per year," "7801 to 7812 times per year," "7813 to 7824 times per year," "7825 to 7836 times per year," "7837 to 7848 times per year," "7849 to 7860 times per year," "7861 to 7872 times per year," "7873 to 7884 times per year," "7885 to 7896 times per year," "7897 to 7908 times per year," "7909 to 7920 times per year," "7921 to 7932 times per year," "7933 to 7944 times per year," "7945 to 7956 times per year," "7957 to 7968 times per year," "7969 to 7980 times per year," "7981 to 7992 times per year," "7993 to 8004 times per year," "8005 to 8016 times per year," "8017 to 8028 times per year," "8029 to 8040 times per year," "8041 to 8052 times per year," "8053 to 8064 times per year," "8065 to 8076 times per year," "8077 to 8088 times per year," "8089 to 8100 times per year," "8101 to 8112 times per year," "8113 to 8124 times per year," "8125 to 8136 times per year," "8137 to 8148 times per year," "8149 to 8160 times per year," "8161 to 8172 times per year," "8173 to 8184 times per year," "8185 to 8196 times per year," "8197 to 8208 times per year," "8209 to 8220 times per year," "8221 to 8232 times per year," "8233 to 8244 times per year," "8245 to 8256 times per year," "8257 to 8268 times per year," "8269 to 8280 times per year," "8281 to 8292 times per year," "8293 to 8304 times per year," "8305 to 8316 times per year," "8317 to 8328 times per year," "8329 to 8340 times per year," "8341 to 8352 times per year," "8353 to 8364 times per year," "8365 to 8376 times per year," "8377 to 8388 times per year," "8389 to 8400 times per year," "8401 to 8412 times per year," "8413 to 8424 times per year," "8425 to 8436 times per year," "8437 to 8448 times per year," "8449 to 8460 times per year," "8461 to 8472 times per year," "8473 to 8484 times per year," "8485 to 8496 times per year," "8497 to 8508 times per year," "8509 to 8520 times per year," "8521 to 8532 times per year," "8533 to 8544 times per year," "8545 to 8556 times per year," "8557 to 8568 times per year," "8569 to 8580 times per year," "8581 to 8592 times per year," "8593 to 8604 times per year," "8605 to 8616 times per year," "8617 to 8628 times per year," "8629 to 8640 times per year," "8641 to 8652 times per year," "8653 to 8664 times per year," "8665 to 8676 times per year," "8677 to 8688 times per year," "8689 to 8700 times per year," "8701 to 8712 times per year," "8713 to 8724 times per year," "8725 to 8736 times per year," "8737 to 8748 times per year," "8749 to 8760 times per year," "8761 to 8772 times per year," "8773 to 8784 times per year," "8785 to 8796 times per year," "8797 to 8808 times per year," "8809 to 8820 times per year," "8821 to 8832 times per year," "8833 to 8844 times per year," "8845 to 8856 times per year," "8857 to 8868 times per year," "8869 to 8880 times per year," "8881 to 889

## Analytic Methodology

The original NHEFS cohort consisted of 8596 women, of whom 83% were white. We initially identified 131 incident breast cancers in NHEFS, 111 from hospital records and 20 from death certificates.

In this study (Schatzkin et al. 1987), women were excluded from the original cohort as follows: 30 women were excluded because baseline information on drinking was missing; 281 women who were pregnant or breast-feeding at the time of the NHANES I interview were excluded, since alcohol consumption was likely to have been affected by these conditions; 675 of the eligible women could not be traced; 483 women were found to be alive but did not have a follow-up interview, either because they refused to participate or could not be contacted; 12 women were considered to be prevalent cases at baseline. A small number of women fell into more than one of these exclusion categories.

After these exclusions the population available for analysis consisted of 7188 women, of whom 121 developed breast cancer. The median follow-up time for the cohort was 10 years.

We were concerned that the breast cancer rate in this cohort should be at least roughly comparable to that in other U.S. populations. Therefore, we applied the age- and race-specific incidences derived from the Connecticut Cancer Registry to our cohort. The ratio of observed to expected cases was 1.07 (95% confidence interval, 0.89–1.28).

Questions on frequency and quantity of alcohol consumption were asked during the baseline interview. Each woman was asked if she had at least one drink of beer, wine, or liquor during the previous year. If she had, she was then asked how often she drank (the possible responses being every day, just about every day, about two or three times per week, about one to four times per month, more than three but less than 12 times per year, or no more than two or three times per year). Those women reporting having had at least one drink in the previous year were also asked how much they usually drank per 24-hour period (in glasses or drinks). We calculated the average number of ounces of ethanol consumed per day by the formula (number of drinks per day)  $\times$  (a drinking frequency factor)  $\times$  (0.5 oz). The factor 0.5 oz was an estimate of the amount of ethanol in a "shot" of liquor, a 5-oz glass of wine, or a 12-oz glass of beer. The frequency factors were as follows: 1 for drinking every day, 5/7 for just about every day, 5/14 for two to three times per week, 5/60 for one to four times per month, 15/730 for 3 to 12 times per year, and 5/730 for two to three times per year. Ounces of ethanol were converted into grams, with one ounce being approximately equal to 25 grams (or roughly two drinks).

Unfortunately, information on quantity of the specific type of alcoholic beverage consumed was not available. Since questions on drinking at earlier ages were asked in the follow-up interview, we attempted a case-control analysis of the relation of drinking at various ages to risk of breast cancer. However, the number of women with breast cancer who provided this information in the follow-up survey was too small for stable analysis.

Information on most of the important covariates, including age, education, poverty index ratio, body mass index, parity, age at menarche, age at menopause, and diet, was provided in the baseline interview. The dietary data came from a 24-hour recall interview conducted by a trained nutritionist using three-dimensional graduated food portion models (National Center for Health Statistics 1972). Standard data on food composition were used for calculation of nutrient intake (Watt and Merrill 1963). Information on family history of breast cancer (in mother or sister) and age at birth of first child was available only from the follow-up interview. Information was collected on smoking at baseline from only 43% of women in the original NHEFS cohort. For those women lacking smoking data at baseline, we inferred smoking status at baseline from the follow-up information. A woman without baseline smoking data who reported at follow-up, for example, that she was a current smoker and that she began smoking 20 years before her baseline examination would have been classified as a current smoker at baseline, with a 20-year duration of smoking.

We found that the distributions of alcohol consumption and most risk factors for breast cancer were virtually identical in the NHEFS cohort used in our analyses and the total NHEFS cohort. The analytic cohort was slightly older than the total cohort (26% vs. 23%  $\geq 65$  years of age) and had a slightly greater proportion of postmenopausal women (52% vs. 47%).

#### Observed Correlations between Alcohol Use and Breast Cancer

The mean age at baseline of women in our analytic cohort was 49 years. Fifty-five percent were under 50, and 25% were over 65 years of age. Women who developed breast cancer were older than those who did not; mean baseline ages were 56 years for cases and 49 years for noncases. Of the 7188 women in the analytic cohort, 42% had not graduated from high school at baseline, whereas 21% had completed more than 12 years of education.

We examined the relation of alcohol consumption to a number of risk factors for breast cancer (Table 5-1). Younger women reported more drinking than older women. The age-adjusted proportions of women reporting drinking were higher among women with more education, lower body mass index, older age at first birth, and lower parity; those who smoked and had a higher fat intake also reported more alcohol use. There was little difference in reported frequency of drinking according to menopausal status, family history of breast cancer, or age at menarche.

Crude incidences of breast cancer according to category of drinking were calculated by the formula (number of cases of breast cancer among women in the category)/(total number of person-years contributed by women in that category). The number of person-years contributed by an individual woman was calculated from baseline to the time of diagnosis of breast cancer, death, or the follow-up interview, whichever came first.

Age-adjusted incidences are shown in Fig. 5-1. The incidence was higher among drinkers than among nondrinkers, and it increased moderately with amount of alcohol consumed.

**Table 5-1** Relative

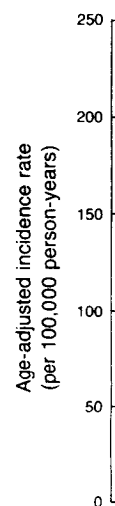
Relative risk estimates

Age-adjusted\*  
(95% Confidence inter  
Multivariate†  
(95% Confidence inter

Source: This table is repri

\*Based on age-adjusted re

†Based on 88 cases with co  
(combined second through  
through fifth quintiles; 34.  
 $\geq 25$ ), age of menarche ( $\leq$



**Fig. 5-1.** Age-adjusted incidence rates of breast cancer by amount of alcohol consumed. These rates have been calculated on the basis of the crude rates for women aged 20 to 74 years from the NHEFS cohort by the direct method. The incidence rates are 118, 148, 188, and 218, respectively, for nondrinkers, 1-2 drinks/week, 3-4 drinks/week, and 5+ drinks/week (based on 1987.)

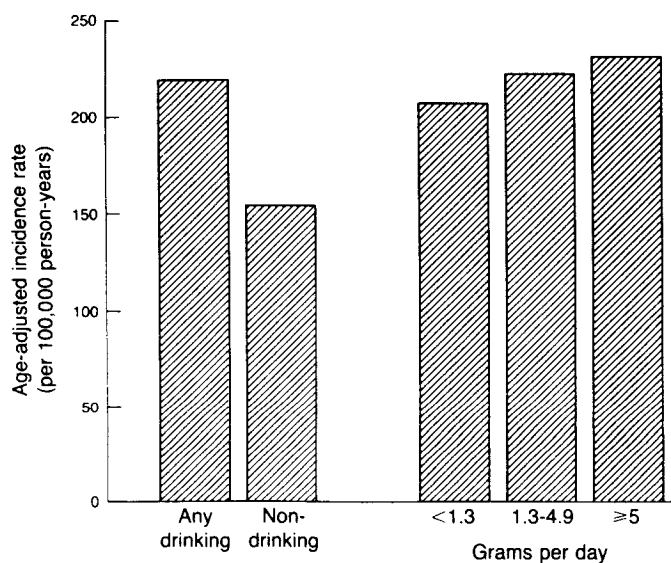
**Table 5-1** Relationship Between Levels of Alcohol Intake and Risk of Breast Cancer

Relative risk estimates	Alcohol intake level (grams per day)				
	None	Any	>0-1.2	1.3-4.9	>5
Age-adjusted*	1.0	1.5	1.4	1.5	1.6
(95% Confidence interval)		(1.1-2.2)	(0.9-2.3)	(0.9-2.6)	(1.0-2.7)
Multivariate†	1.0	1.6	1.4	1.6	2.0
(95% Confidence interval)		(1.0-2.5)	(0.8-2.5)	(0.9-3.1)	(1.1-3.7)

Source: This table is reprinted with permission of *The New England Journal of Medicine*.

\*Based on age-adjusted regression coefficients from the proportional-hazards models (121 cases).

†Based on 88 cases with complete covariate informatics, including age (years); education (>12 years); body mass index (combined second through fourth quintiles 21-29; fifth quintile, >30); total dietary fat (grams per day) (separate second through fifth quintiles; 34.2-47.5; 47.6-61.4; 61.5-80.6; ≥80.7); age at first parturition (19-20, 21-22, 23-24, and ≥25), age of menarche (≤12), parity (nulliparity, one or two births), positive family history; and premenopausal status.



**Fig. 5-1.** Age-adjusted rates of breast cancer according to level of alcohol consumption. These rates have been age-adjusted by the indirect method (Fleiss 1981), on the basis of the crude and age-specific incidence rates for breast cancer among women 25 to 74 years of age from the Connecticut Cancer Registry. Age-adjusted rates calculated by the direct method (Fleiss 1981) (on the basis of the analytic cohort) were 150 and 218, respectively, for no drinking and any drinking, and 206, 204, 271 for the lowest through the highest levels of drinking. Five grams of ethanol per day is roughly equivalent to three drinks per week. (Figure modified from Schatzkin, Jones, Hoover, et al., 1987.)

To analyze the simultaneous relation of alcohol, age, and other variables to incidence of breast cancer in the cohort, we used Cox's proportional hazards regression technique (Cox and Oakes 1984). The analyses were performed with the PROC PHGLM procedure available in the SAS statistical package (SAS Institute, Inc. 1983). Estimates of relative risk (and 95% confidence intervals) were derived from the regression coefficients (and standard errors of the coefficients) yielded by the regression models.

Table 5-1 depicts the results of proportional-hazards models comprising variables for age and alcohol use only. The estimated relative risk (95% confidence interval) for any drinking compared to nondrinking was 1.5 (1.1-2.2); the estimates for the three tertiles of drinking, from lowest to highest, were 1.4 (0.9-2.3), 1.5 (0.9-2.6), and 1.6 (1.0-2.7), respectively.

We next performed a series of analyses based on various "trivariate" models that included variables for age, alcohol consumption, and one of several potential confounders, including education (<12, 12, >12 years), total dietary fat in grams per day (quintiles), age at first birth (<19, 19-20, 21-22, 23-25, ≥26), age at onset of menarche (≤11, 12, 13, 14, ≥15), parity (nulliparity, one, two, three, or more than four live births), family history of breast cancer, menopausal status, body mass index (quintiles), or cigarette smoking (never, former, current smoker; or, 0, 1-13, or >13 pack-years). These analyses yielded relative risks for the highest tertile of drinking in the range of 1.4 to 2.0. Estimates were largely unchanged when quintile indicators for saturated fat, or fat as a percentage of total calories, were substituted for total fat, nor were they altered in separate analyses that included quintile indicators for protein, dietary cholesterol, or total calories.

Models that simultaneously included a variety of potential confounders generated relative risk estimates (95% confidence intervals) of 1.6 (1.0-2.5) for any drinking compared to nondrinking. For the three tertiles of drinking (relative to nondrinking), the estimates from lowest to highest were 1.4 (0.8-2.5), 1.6 (0.9-3.1), and 2.0 (1.1-3.7) (Table 5-2). (Because of missing information on covariates, especially smoking and dietary variables, the number of cases analyzed in the multivariate regressions was somewhat lower.)

We used the multivariate proportional hazards analysis to examine a linear trend variable for alcohol consumption (with four values: nondrinking and three tertiles of alcohol use). The *p*-value for trend was 0.020 for that variable. In a similar analysis of a linear trend variable limited to the three tertiles of drinking, the *p*-value was 0.50.

Finally, we performed stratum-specific analyses for a number of risk factors to examine the possibility that the relation between alcohol and breast cancer differed across risk factor subgroups. The relative risk estimates for any drinking (relative to nondrinking) were greatest for women under 50, premenopausal women, and women with the lowest body mass index. These three groups had relative risks (95% confidence intervals) of 2.1 (1.1-4.1), 2.0 (1.0-3.8), and 3.5 (1.6-7.9), respectively. Relative risk estimates for any drinking were not materially changed in analyses carried out within categories of age at first birth, parity, age at menarche,

**Table 5-2** Percentage Distribution by Fat Intake According to Risk Factors for Breast Cancer

Risk factor	Fat (g/day) for indicated quartiles				Fat (% of kcal/day) for indicated quartiles			
	<38	38-53.9	54-73.9	>74	<30	30-35.9	36-41.9	>42
Age (years)								
25-34	19	23	25	33	23	26	27	24
35-54	21	22	26	31	21	25	28	26
55-64	30	26	24	20	26	28	23	23
≥65	33	28	24	15	28	27	24	21
Poverty index ratio* (≥3.75 top quartile)	20	26	25	29	23	29	26	22
Body mass index* (≥30.0 top quartile)	32	26	21	21	26	25	24	25
Age at menarche* (<12 years)	24	25	27	24	24	27	25	24
Premenopausal*	18	23	29	30	24	22	32	22
Family history of breast cancer (first degree relative)*	22	26	27	25	26	27	25	22

\*Age-adjusted.

WILLIAMS & WILKINS

family history of breast cancer, fat consumed (grams per day or percentage of total calories), or smoking.

### Discussion

This investigation using the NHEFS data set showed a 50–100% elevation in risk of breast cancer for women who reported any drinking. The data were consistent with a modest dose–response relation across the levels of alcohol consumption (Schatzkin et al. 1987).

It is noteworthy that women in the NHEFS cohort were relatively light drinkers; only 9% consumed one or more drinks per day. Too few women in the NHEFS cohort reported heavy drinking for us to determine whether heavier drinking conferred an even greater excess risk of breast cancer.

Controlling for a number of potentially confounding covariates did not eliminate the association between alcohol and breast cancer. However, controlling for dietary factors in NHEFS is problematic. This limitation is of some importance because dietary factors have been implicated in the etiology of breast cancer and dietary intake is correlated with alcohol consumption. The assessment of a woman's "usual" intake by the 24-hour recall method is limited by the substantial day-to-day variation in what is eaten (Block 1982). Considerable misclassification can occur when this method is used for assignment of individuals to quintiles of nutrient intake (Freudenheim et al. 1987). Although it has become generally accepted that random misclassification in the exposure variable (alcohol in this case) results in dilution of the relative risk toward no association (Rothman 1986), the less extensive literature on misclassification of a confounder indicates that the effect on the relative risk can be in either direction (Greenland and Robins 1985). Since the number of cases in this study was relatively small, we cannot rule out the possibility that misclassification of dietary intake could have resulted in inadequate control of confounding.

Adequate information on a history of benign breast disease was not available from the NHEFS data set. However, there is little evidence for an association between alcohol use and benign breast disease, and in other cohort studies a history of benign breast disease did not confound the positive relation between alcohol and breast cancer (Hiatt and Bawol 1984; Willett et al. 1987; Hiatt et al. 1988). Therefore, it is unlikely that confounding by a history of benign breast disease could account for our findings.

With regard to our findings of a stronger association between alcohol and breast cancer in younger, leaner, and premenopausal women, it is of interest that the risk of breast cancer associated with drinking was greater in those women with the least risk at baseline (i.e., younger and possibly leaner women). Alternatively, the higher risk in younger women might simply reflect a harmful effect of drinking at earlier, as opposed to later, ages, as has been suggested by a recent case-control study (Harvey et al. 1987). This latter hypothesis can be tested later with the NHEFS data set, since questions on the amount of drinking at various ages were asked in the follow-up interview. In the future, when the number of cases with

information on early drinking relationship between breast cancer carried out.

### DIETARY FAT AND BREAST

Laboratory (Tannenbaum correlation (Armstrong and 1973; Enig, Munn, and Kesson 1979; Hirayama 1978; suggested that consumption cancer, but the evidence suggests that when both fat intake contributes to incidence (Kritchevsky et al. 1986). The strongest support for the role of fat is difficult to disentangle from fat intake. Some case-control studies (Hirohata et al. 1985; Miller 1986; Katsouyanni et al. 1986; Lubin 1986; Phillips 1975) have shown no positive association (questionnaire) and subsequent

### Analytic Methodology

The criteria for exclusion of those used in the study of the criteria described earlier. Initially 200 women were obtained at baseline, 100 whose dietary information was collected the data, and 117 who were pregnant or breast feeding. 776 who were lost to follow-up because they refused to participate.

Breast cancer was identified (the effects of alcohol were reviewed in detail.) Ninety-

information on early drinking becomes larger, a case-control analysis of the relationship between breast cancer and drinking at earlier versus later ages can be carried out.

#### DIETARY FAT AND BREAST CANCER

Laboratory (Tannenbaum 1942; Carroll and Khor 1970; Carroll 1980) and human correlation (Armstrong and Doll 1975; Carroll and Khor 1975; Drasar and Irving 1973; Enig, Munn, and Keeney 1978; Gaskill et al. 1979; Gray, Pike, and Henderson 1979; Hirayama 1978; Ingram 1981; Lea 1965; Miller et al. 1978) studies have suggested that consumption of large amounts of fat predisposes women to breast cancer, but the evidence is far from conclusive. Some recent experimental work suggests that when both fat and total energy intake are considered, total energy intake contributes to incidence of mammary cancer (Kritchevsky et al. 1984; Kritchevsky et al. 1986). Inter- and intranational ecologic studies provide some of the strongest support for the hypothesis linking dietary fat to breast cancer, but again it is difficult to disentangle total energy intake (and intake of other nutrients) from fat intake. Some case-control studies have estimated dietary fat (Graham et al. 1982; Hirohata et al. 1985; Miller et al. 1978; Nomura et al. 1985); others have provided information on consumption of certain foods or food groups high in fat (Hislop et al. 1986; Katsouyanni et al. 1986; Kinlen 1982; Le et al. 1986; Lubin et al. 1981; Lubin 1986; Phillips 1975; Talamini et al. 1984) and have produced inconsistent results. A study of a Japanese cohort found that meat consumption was associated with an increased risk of breast cancer (Hirayama 1978), but another study among Seventh Day Adventists in the United States did not find this association (Phillips and Snowdon 1983). A recent large cohort study of over 600 cases of breast cancer showed no positive association between dietary fat (as assessed by a food frequency questionnaire) and subsequent breast cancer (Willett et al. 1987).

#### Analytic Methodology

The criteria for exclusion of women from this study were somewhat different from those used in the study of the relation between alcohol and breast cancer that was described earlier. Initially excluded were 1727 women from whom no dietary data were obtained at baseline, 205 whose dietary data were obtained from a proxy, 35 whose dietary information was considered "unsatisfactory" by the nutritionist collecting the data, and 117 with imputed data. Also excluded were 244 women who were pregnant or breast feeding, seven with prevalent breast cancer at baseline, and 776 who were lost to follow-up either because they could not be traced or because they refused to participate. The final analytic cohort consisted of 5485 women.

Breast cancer was identified by the same procedures as those used in the study of the effects of alcohol use. (All hospital records indicating breast cancer were reviewed in detail.) Ninety-nine cases were identified: 84 from hospital records and

15 from death certificates. The ratio of observed to expected cases, again based on the age- and race-specific incidences of breast cancer from the Connecticut Tumor Registry, was 0.93 (0.75–1.13). Thirty-four cases were premenopausal, and 65 were postmenopausal at baseline.

Dietary exposure data were the same as those described in the preceding section of this chapter. The key variables in the study of the link between fat intake and breast cancer were intakes of total fat, percent of energy intake derived from fat, and intakes of monounsaturated fat and of cholesterol. Ten persons for whom we had no data on fatty acid and cholesterol intake were excluded from all analyses of these dietary variables. Information on other covariates was obtained as described in the study of alcohol consumption.

#### Observed Correlations between Fat Intake and Breast Cancer

In Table 5–2 we present data on the distribution of age groups and age-adjusted distribution of several risk factors for cancer across categories of dietary fat. Younger women tended to report total fat intakes in the upper quartiles and older women in the lower quartiles. This pattern reflected, in part, the fact that younger women reported larger energy intakes than did older women, since the trend was weakened considerably when fat intake as a percentage of energy was examined. Women with higher relative income and premenopausal women were found disproportionately in the higher quartiles of fat intake. Relatively overweight women, however, had total fat intakes concentrated in the two lower quartiles. Little association was seen between fat intake and either age at menarche or family history of breast cancer. For fat as a percentage of total caloric intake, no association was seen for these two risk factors for breast cancer.

Mean intakes of fat for cases and noncases are presented in Table 5–3. These mean values were adjusted for age and other risk factors for breast cancer risk by

**Table 5–3** Comparison of Mean Daily Nutrient Intakes Between Cases and Noncases of Breast Cancer\*

Nutrients (units)	Age-adjusted		Full model†	
	Cases (n = 99)	Noncases (n = 5386)	Cases (n = 86)	Noncases (n = 4912)
Fat (g)	57.0 (3.2)	59.9 (0.4)	55.0 (3.4)	60.3 (0.5)
Fat (% of energy)	34.6 (0.9)	36.0 (0.1)	34.6 (0.9)	36.0 (0.1)
Energy (kcal)	1441 (61)	1465 (8)	1404 (65)	1475 (9)
Saturated fat (g)	20.0 (1.3)	21.4 (0.2)	19.4 (1.4)	21.5 (0.2)
Polyunsaturated fat (g)	6.6 (0.6)	6.6 (0.1)	6.1 (0.6)	6.7 (0.1)
Monounsaturated fat (g)	21.8 (1.3)	22.9 (0.2)	21.0 (1.4)	23.1 (0.2)
Cholesterol (mg)	282 (24)	305 (3)	268 (26)	305 (3)

Note: No statistically significant differences were found in any of these nutrient comparisons.

\*Standard error of the mean in parentheses.

†Model includes age, poverty index ratio, body mass index, age at menarche, menopausal status/age at menopause, and family history of breast cancer. Analyses were done on a subset of women with complete information.

means of general linear variable, with age and the indicator variable. (Because from fat were skewed to logarithmic transformed, therefore, the untransformed cases was less than that differences were not statistically significant.)

Estimates of relative hazards regression quartiles for fat intake are than those in the lowest intervals) for women in the 0.67), respectively, for intake (for a protective association saturated fat). The trend marginally significant (p = 0.08) and energy variables showed

Analyses according to protective effect of high fat risk, 0.08; 95% confidence interval protective effect was still 0.30–1.54), but the confidence interval

When the relation between mass index, nonsignificant quartile of fat intake: For confidence interval) value 28.0, the values were 0.041 (0.11–1.47).

#### Discussion

We found no positive association in the NHEFS data set. In relation. These findings are (al. 1987).

Again, the potential hour recall must be considered interest. Since random misclassification toward a relative risk of breast cancer and several misclassification.

The NHANES I data obesity and energy intake finding is differential un-

means of general linear regression, with the dietary variables as the dependent variable, with age and the other risk factors as covariates, and with case status as an indicator variable. (Because all the dietary variables except percentage of energy from fat were skewed to the right, the regression analyses were repeated with use of logarithmic transformed values. The results of both analyses were similar; therefore, the untransformed results are presented here.) Although the mean intake for cases was less than that for noncases for each of the dietary variables, these differences were not statistically significant.

Estimates of relative risk (and 95% confidence intervals) derived from proportional hazards regression models are presented in Table 5-4. Women in the upper quartiles for fat intake and for saturated fat intake had a lower risk of breast cancer than those in the lowest quartile. The multivariate relative risks (95% confidence intervals) for women in the upper quartiles were 0.34 (0.16-0.73) and 0.29 (0.12-0.67), respectively, for intakes of total and saturated fat. The multivariate trend tests (for a protective association) were significant ( $p = 0.03$  for fat,  $p = 0.04$  for saturated fat). The trend test for fat as a percentage of total energy yielded a marginally significant (protective) result ( $p = 0.06$ ). None of the other dietary fat and energy variables showed an association with incidence of breast cancer.

Analyses according to baseline menopausal status demonstrated that the protective effect of high fat intake was strongest in premenopausal women (relative risk, 0.08; 95% confidence interval, 0.01-0.61). In postmenopausal women, the protective effect was still apparent (relative risk, 0.63, 95% confidence interval, 0.30-1.54), but the confidence interval now included 1.0.

When the relation between fat intake was examined within tertiles of body mass index, nonsignificant protective associations were observed for the highest quartile of fat intake: For body mass index of 22.0 or less, the relative risk (95% confidence interval) values were 0.65 (0.17-2.52); for body mass index of 22.1-28.0, the values were 0.08 (0.01-0.65); and for body mass index of 28.1 or more, 0.41 (0.11-1.47).

## Discussion

We found no positive association between dietary fat intake and risk of breast cancer in the NHEFS data set. If anything, the data are consistent with a slight inverse relation. These findings are qualitatively similar to those of Willett et al. (Willett et al. 1987).

Again, the potential misclassification of dietary intake resulting from the 24-hour recall must be considered. In this study dietary variables were the exposure of interest. Since random misclassification would tend to reduce a positive association toward a relative risk of 1.0, it is plausible that the lack of association between breast cancer and several of the dietary variables could have resulted from such misclassification.

The NHANES I data seem to indicate a slight negative association between obesity and energy intake in women (Braitman et al. 1985). One explanation for this finding is differential underreporting of intake by the obese who might be at in-

**Table 5-4** Relationship Between Dietary Fat and Energy Intake and the Occurrence of Breast Cancer

Variable	Age-adjusted			Full model*		
	No. of cases (n = 99)	No. of noncases (n = 5386)	Relative risk (95% confidence interval)†	No. of cases (n = 86)	No. of noncases (n = 4912)	Relative risk (95% confidence interval)†
<b>Fat (g)‡</b>						
≤38	33	1337	1.00	29	1198	1.00
38-53.9	24	1313	0.78 (0.46-1.33)	21	1194	0.73 (0.42-1.29)
54-73.9	29	1350	0.95 (0.58-1.58)	27	1234	0.96 (0.57-1.63)
≥74	13	1386	0.47 (0.25-0.91)	9	1286	0.34 (0.16-0.73)
			p for trend = 0.07			p for trend = 0.03
<b>Fat (% of energy)‡</b>						
<30	26	1277	1.00	22	1157	1.00
30-35.9	38	1397	1.38 (0.84-2.27)	35	1279	1.50 (0.88-2.56)
36-41.9	20	1403	0.77 (0.43-1.38)	16	1292	0.73 (0.38-1.38)
≥42	15	1309	0.62 (0.33-1.19)	13	1184	0.66 (0.33-1.31)
			p for trend = 0.05			p for trend = 0.06
<b>Energy (kcal)‡</b>						
<1030	26	1338	1.00	23	1193	1.00
1030-1378.9	31	1337	1.23 (0.73-2.08)	28	1209	1.23 (0.71-2.13)
1379-1775.9	24	1349	0.99 (0.57-1.71)	21	1260	0.89 (0.49-1.63)
≥1776	18	1362	0.87 (0.47-1.61)	14	1250	0.70 (0.36-1.40)
			p for trend = 0.54			p for trend = 0.22
<b>Saturated fat (g)‡</b>						
<13	34	1431	1.00	29	1282	1.00
13-18.9	23	1275	0.81 (0.47-1.37)	21	1176	0.83 (0.47-1.45)
19-26.9	30	1287	1.07 (0.65-1.76)	29	1172	1.18 (0.70-1.98)
≥27	12	1383	0.44 (0.23-0.86)	7	1272	0.29 (0.12-0.67)
			p for trend = 0.07			p for trend = 0.04
<b>Polyunsaturated fat (g)‡</b>						
<3	31	1398	1.00	27	1229	1.00
3-4.9	19	1144	0.78 (0.44-1.37)	17	1065	0.75 (0.41-1.38)
5-8.9	28	1555	0.90 (0.54-1.50)	26	1423	0.93 (0.54-1.59)
≥9	21	1279	0.93 (0.53-1.63)	16	1185	0.73 (0.39-1.36)
			p for trend = 0.05			p for trend = 0.05

0.70 (0.36-1.40)  
p for trend = 0.22

1250

14

0.87 (0.47-1.61)  
p for trend = 0.54

1362

18

# Saturated fat (g)†

<13	34	1431	1.00	29	1282	1.00
13-18.9	23	1275	0.81 (0.47-1.37)	21	1176	0.83 (0.47-1.45)
19-26.9	30	1287	1.07 (0.65-1.76)	29	1172	1.18 (0.70-1.98)
≥27	12	1383	0.44 (0.23-0.86)	7	1272	0.29 (0.12-0.67)
			p for trend = 0.07			p for trend = 0.04

# Polyunsaturated fat (g)†

<3	31	1398	1.00	27	1229	1.00
3-4.9	19	1144	0.78 (0.44-1.37)	17	1065	0.75 (0.41-1.38)
5-8.9	28	1555	0.90 (0.54-1.50)	26	1423	0.93 (0.54-1.59)
≥9	21	1279	0.93 (0.53-1.63)	16	1185	0.73 (0.39-1.36)
			p for trend = 0.85			p for trend = 0.45

# Monounsaturated fat (g)†

<14	31	1365	1.00	28	1225	1.00
14-19.9	24	1222	0.90 (0.53-1.53)	20	1124	0.82 (0.46-1.45)
20-28.9	25	1415	0.81 (0.48-1.38)	24	1318	0.83 (0.48-1.43)
≥29	19	1338	0.74 (0.41-1.34)	14	1235	0.59 (0.30-1.13)
			p for trend = 0.28			p for trend = 0.14

# Cholesterol (mg/dl)†

<130	25	1333	1.00	11	1197	1.00
130-232.9	31	1321	1.29 (0.76-2.18)	30	1221	1.33 (0.76-2.31)
233-414.9	24	1370	0.95 (0.54-1.66)	19	1261	0.79 (0.43-1.46)
≥415	19	1352	0.80 (0.44-1.47)	15	1223	0.70 (0.36-1.37)
			p for trend = 0.32			p for trend = 0.12

\*Full model includes age, poverty index ratio, body mass index, age at menarche, menopausal status/age at menopause, and family history of breast cancer. Analyses were done on subset of women with complete information.

†Relative risks (95% confidence intervals) for the proportional hazards model.

‡Age-adjusted.

creased risk of breast cancer. This underreporting is considered unlikely because of the careful and standardized dietary assessment techniques used in that survey (Braitman et al. 1985). Furthermore, if underreporting by more overweight women were the explanation for the overall findings regarding any relation between fat and breast cancer, then one would expect no association between dietary fat and breast cancer to be evident in the leaner tertiles. The fact that the point estimates for fat intake were substantially less than 1.0 for each of the tertiles of body mass index argues against this underreporting explanation.

In addition to expressing fat intake as a percentage of calories, other means of adjusting fat intake for body size and energy intake include examining fat intake per kilogram body weight and examining residuals of fat after regressing calories (on fat). We found that both of these approaches yielded results similar to those obtained when fat was assessed as a percentage of caloric intake, with multivariate relative risk estimates for the upper quartile, relative to the lowest quartile, of 0.66 for fat/kg of body weight and of 0.68 for fat residuals. The confidence intervals for both point estimates included 1.0.

We should note, especially given the results of the analysis of the relationship between alcohol consumption and breast cancer in the NHEFS data set as well as the findings from other studies (Harvey et al. 1987; Hiatt and Bawol 1984; Hiatt et al. 1987; La Vecchia et al. 1985; Le et al. 1984; O'Connell et al. 1987; Rosenberg et al. 1982; Talamini et al. 1984; Willett et al. 1987), that controlling for alcohol consumption did not materially affect the association between fat intake and breast cancer.

Since it is conceivable that different effects of dietary fat on incidence and on survival could have influenced our results, we performed similar analyses after exclusion of the 15 cases identified from death certificates only, with date of death used as date of incidence. Although the numbers were obviously much smaller, the same inverse association between breast cancer and high intake of fat was seen in cases determined by death certificates as in those identified through hospital records.

Two additional limitations merit discussion. First, the women in this study are generally consumers of a large amount of fat, certainly in relation to the levels consumed in some other countries (e.g., Japan). Therefore, if there were a substantially reduced risk of breast cancer at lower levels of dietary fat intake (e.g., 20% of energy), one would not be able to observe this protective effect in the NHEFS data set. Second, data on exposure in early life to dietary fat and other nutrients were not available.

#### SERUM CHOLESTEROL AND CANCER

In this third investigation in the epidemiology of cancer done with the NHEFS data set, we consider men as well as women, incidence at sites other than the breast, incidence at all sites combined, and total mortality attributable to cancer (Schatzkin et al. 1987).

The relation between cholesterol and cancer, particularly breast cancer, has been a controversial topic. A number of studies have reported an association between cholesterol and cancer, particularly breast cancer (e.g., Braitman et al. 1980; Cambien et al. 1980; International Collaborative Group 1980; Kozarevic et al. 1980; Rose and Shipley 1980; Williams et al. 1980). However, other studies have reported no such inverse relationship (e.g., Hiatt et al. 1981; Hiatt et al. 1983; Salonen 1982; Nicolaysen 1972; Willett et al. 1987). The association between cholesterol and cancer in women has been reported by Hiatt and Fireman (1982; Wallace et al. 1982) as a nonsignificant inverse association (Feinleib 1982) and between level of cholesterol and cancer in men (Tornberg et al. 1982).

Since a few studies have reported an association between cholesterol and cancer in women (e.g., Hiatt and Fireman 1982; Shipley 1980; Sherris 1980), we suggested a "preclinical" association between cholesterol by undiagnosed disease (e.g., 1980; McMichael et al. 1980) as inconsistent. Some studies have reported malignancies diagnosed by cholesterol in serum (e.g., Smith, and Hames 1980).

#### Analytic Methodology

The procedure for incidence and mortality was described earlier. The expected number of cases from the Connecticut Cancer Registry (0.95–1.14). The confidence interval for women was 1.01 (0.95–1.14).

Criteria for exclusion of cases from incidence and mortality data were: women could not be contacted or because of baseline data on serum cholesterol.

The relation between serum cholesterol and cancer has long been a controversial topic. A number of cohort studies have found that among men, serum cholesterol and cancer, particularly cancer of the colon, are inversely related (Beaglehole et al. 1980; Cambien et al. 1980; Feinleib 1981; Garcia-Palmieri et al. 1981; International Collaborative Group 1982; Kagan et al. 1981; Kark, Smith, and Hames 1980; Kozarevic et al. 1981; Morris et al. 1983; Peterson and Trell 1983; Rose et al. 1974; Rose and Shipley 1980; Sherwin et al. 1987; Stemmerman et al. 1981; Wallace et al. 1982; Williams et al. 1981). A number of other cohort studies, though, found no such inverse relation, either for all cancer or for cancer of the colon (Dyer et al. 1981; Hiatt et al. 1982; Hiatt and Fireman 1986; Keys et al. 1985; Morris et al. 1983; Salonen 1982; Sorlie and Feinleib 1982; Thomas et al. 1982; Westlund and Nicolaysen 1972; Wingard et al. 1984; Yaari et al. 1981). Most studies of cholesterol and cancer in women have reported no significant association (Dyer et al. 1981; Hiatt and Fireman 1986; Kark et al. 1980; Morris et al. 1983; Sorlie and Feinleib 1982; Wallace et al. 1982; Wingard et al. 1984), although a few studies have shown a nonsignificant inverse (Kark, Smith, and Hames 1980; Morris et al. 1983; Sorlie and Feinleib 1982) or direct (Wallace et al. 1982) association. A positive association between level of cholesterol in serum and colorectal cancer has recently been described (Tornberg et al. 1986).

Since a few studies have found that the inverse relation between serum cholesterol and cancer was confined to the first few years of follow-up (Cambien, Ducimiere, and Richard 1980; International Collaborative Group 1982; Rose and Shipley 1980; Sherwin et al. 1987; Wallace et al. 1982), some investigators suggested a "preclinical cancer effect" (i.e., the metabolic depression of serum cholesterol by undiagnosed cancers) as an explanation for the finding (Rose and Shipley 1980; McMichael et al. 1984). Again, the data on this particular hypothesis are inconsistent. Some studies found that the inverse relation did not disappear for malignancies diagnosed 2–15 or more years after measurement of the concentration of cholesterol in serum (Beaglehole et al. 1980; Garcia-Palmieri et al. 1981; Kark, Smith, and Hames 1980; Peterson and Trell 1983; Sorlie and Feinleib 1982).

#### Analytic Methodology

The procedure for identifying incident cases and deaths due to cancer in NHEFS was described earlier. The ratio and 95% confidence interval of observed to expected number of cases (based on age-, gender-, and race-specific incidence rates from the Connecticut Tumor Registry) for all incidence of cancer in men was 1.04 (0.95–1.14). The comparable ratio of observed to expected number of cases among women was 1.01 (0.91–1.11).

Criteria for exclusion of subjects were slightly different for the analyses of incidence and mortality. At the time of NHEFS, 351 eligible men and 675 eligible women could not be traced; 309 men and 483 women were traced and found to be alive but did not have a follow-up interview, either because they could not be contacted or because they refused to participate; and 20 men and 61 women had no baseline data on serum cholesterol. Ten men and 25 women with cancer at any site

(except nonmelanoma skin cancer) at baseline were excluded from the analyses of all cancer. A smaller number of prevalent cases were excluded from the site-specific analyses; the precise number varied from site to site. A few men and women fell into more than one of these exclusion categories. For the analyses of mortality, only those missing baseline data on serum cholesterol and/or those identified as prevalent cases were excluded.

Overall, 5125 men and 7363 women were included in the analysis of incidence with cancers developing in 459 men and 398 women. The analyses of mortality comprised 5791 men and 8535 women, including 258 men and 186 women dying with cancer as the underlying cause.

Concentration of cholesterol in serum was determined from blood specimens obtained from nonfasting subjects; a semiautomated modified ferric chloride-sulfuric acid method was used. Measurements were done in the lipid laboratory of the Centers for Disease Control, Atlanta, Georgia (National Center for Health Statistics 1980; Eavenson et al. 1966); other covariate data were obtained as described in the two preceding sections.

#### Observed Correlations between Serum Cholesterol and Cancer

The mean age at baseline of men in our study population was 52 years; that of women, 48 years. (These simple descriptive data for women are nearly identical to those presented in the section on alcohol consumption and breast cancer, but they are repeated here for comparison with the findings for men and because the cohorts analyzed were slightly different.) Of the 5125 men, 48% did not graduate from high school, whereas 25% had more than 12 years of education; the analogous figures for women were 42% and 21%. Eighty-six percent of the men and 84% of the women were white.

The mean serum cholesterol levels for the entire group ( $\pm$  standard deviation) were 221 ( $\pm$ 47) mg/100 ml for men and 222 ( $\pm$ 50) mg/100 ml for women.

We examined the interrelation of serum cholesterol level with various risk factors for cancer. Among both men and women, high levels of cholesterol in serum at baseline were associated with older age, poverty index ratio, body mass index, cigarette smoking, alcohol assumption, and lower consumption of fiber. There was little difference across levels of serum cholesterol in years of education, race, and, for women, age at first birth, age at menarche, and parity. Intake of fat was directly related to cholesterol in women but essentially unrelated in men.

Age-related incidence and mortality rates (computed by the method described in the study of alcohol consumption-breast cancer) are shown in Fig. 5-2. Among men there was an inverse relation between cholesterol and both incidence of cancer and mortality due to cancer. Among women the inverse relation for mortality was stronger than that for incidence, with elevations in cancer rates being largely confined to those in the lowest quintile of serum cholesterol.

In Fig. 5-3 we present data for those specific sites with at least ten cases in both sexes (except for cancers of the prostate, cervix, endometrium, and ovaries, for which ten cases were required in the appropriate gender group). In men an inverse

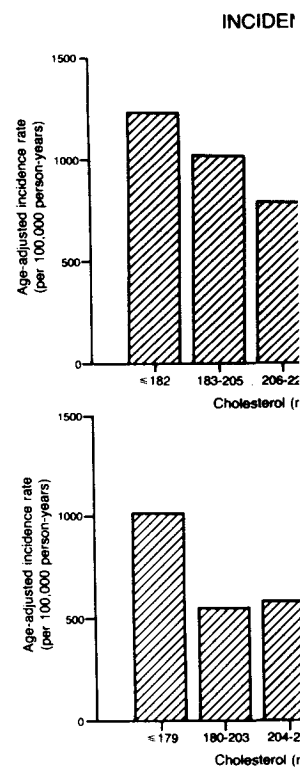


Fig. 5-2. Age-related incidence levels of serum cholesterol (Fleiss 1981) according to

relation can be seen for bladder cancers and for and prostate cancer or ly ent for cancers of the lu relation between cholest ovarian, and uterine co some sites were based (

Age-adjusted and n ards regression models a between cholesterol and estimates (95% confider terol (in comparison to (1.0-2.2), 1.0 (0.7-1.5 dence was significant (j

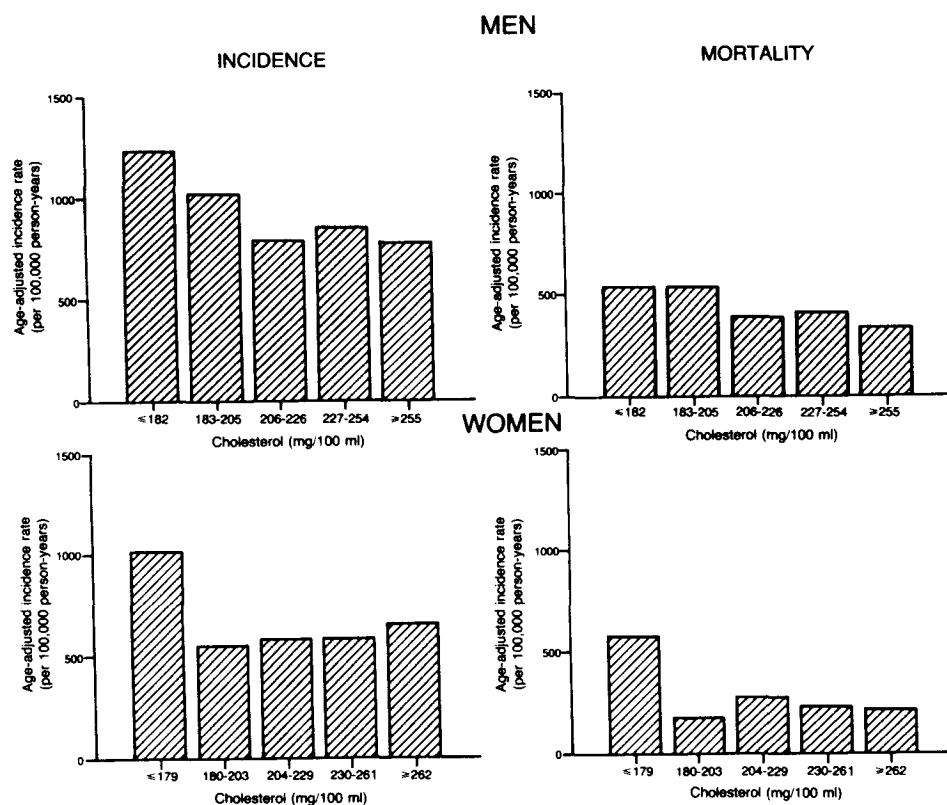
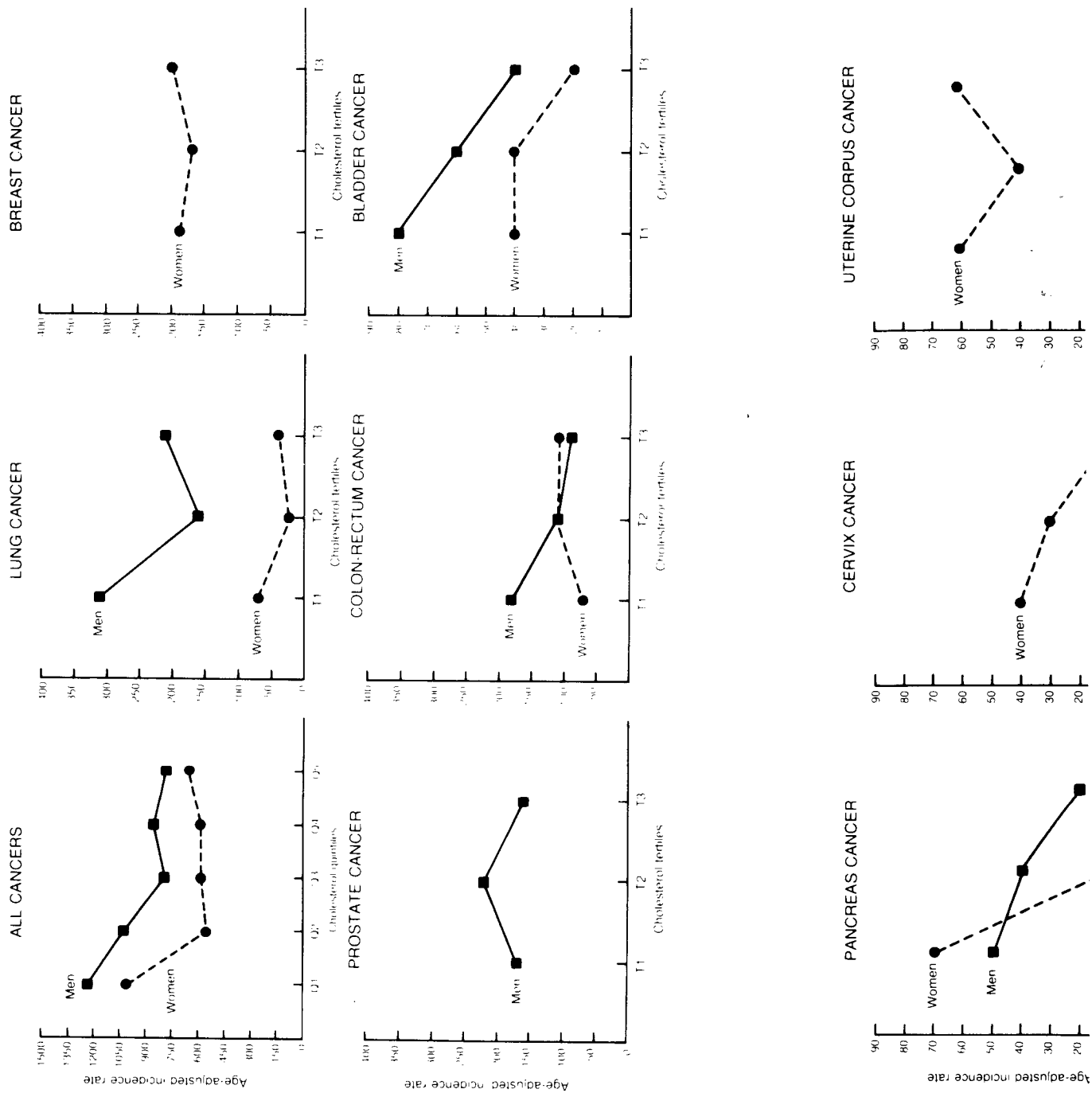


Fig. 5-2. Age-related incidence and mortality rates for cancer of all sites according to levels of serum cholesterol and gender. Rates were age-related by the direct method (Fleiss 1981) according to the age distribution of the cohort.

relation can be seen for all cancers as well as for lung, colorectal, pancreas, and bladder cancers and for leukemia. There was little association between cholesterol and prostate cancer or lymphoma. Among women, inverse associations were apparent for cancers of the lung, pancreas, bladder, and cervix and for leukemia. Little relation between cholesterol level and cancer was evident for breast, colorectal, ovarian, and uterine corpus cancers. (Note, however, that the incidence rates for some sites were based on a small number of cases within cholesterol levels.)

Age-adjusted and multivariate estimates of relative risk from proportional hazards regression models are presented in Table 5-5. There was an inverse association between cholesterol and incidence of cancer in men; the multivariate relative risk estimates (95% confidence intervals) for the first through fourth quintiles of cholesterol (in comparison to the highest quintile) were, respectively, 1.7 (1.2-2.6), 1.5 (1.0-2.2), 1.0 (0.7-1.5), and 1.2 (0.8-1.8). The multivariate trend test for incidence was significant ( $p = 0.003$ ). Similar results were obtained when mortality



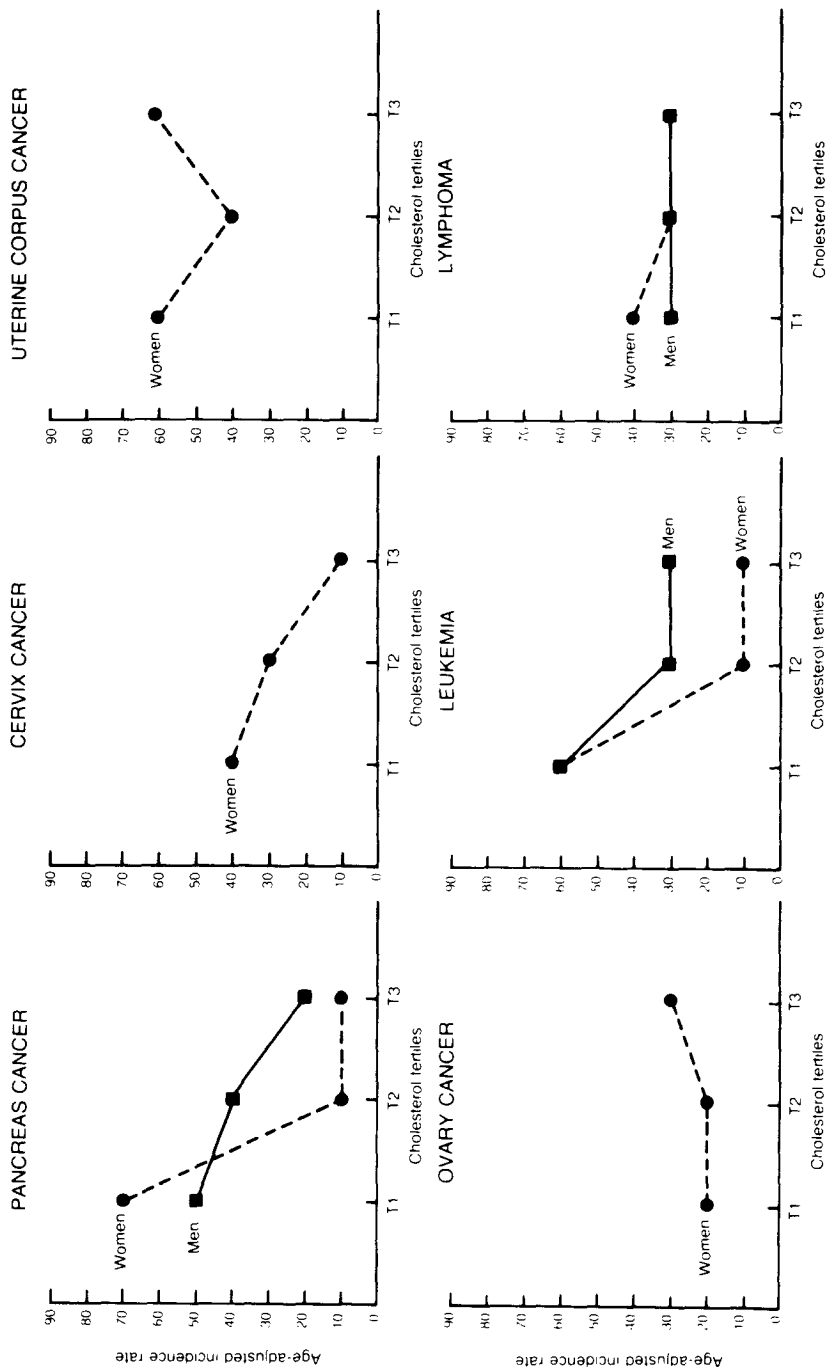


Fig. 5-3. Age-adjusted, site-specific incidence of cancer according to level of serum cholesterol and gender. The first through third tertiles of cholesterol (mg/100 ml) are defined as follows: for men,  $\leq 200$ ,  $201-235$ ,  $\geq 236$ ; for women,  $\leq 196$ ,  $197-239$ ,  $\geq 240$ .

**Table 5-5** Relationship Between Level of Serum Cholesterol and Cancer in All Sites According to Gender

[illegible]

\*Aged-adjusted in proportional hazards model that included variables for age and cholesterol.

Model includes variables for age, education, body mass index, smoking (pack-years), alcohol, dietary fat as a percentage of total calories, dietary fiber, and cholesterol. Because some subjects lacked information on smoking (even when follow-up data were used) and/or diet, the number of cases in the multivariate models for incidence and mortality was reduced to 257 and 127, respectively.

The Model includes variables for age, education, smoking (pack-years), alcohol, dietary fat as a percentage of total calories, age at first birth, age at menarche, parity, and cholesterol. Because some subjects lacked information on smoking (even when follow-up data were used) and/or diet, the number of cases in the multivariate models for incidence and mortality was reduced to 268 and 107, respectively.

was analyzed and when eliminated.

For incidence of cancer in risk confined to the low relative risk estimates for 0.8 (0.6–1.2), and 0.9 (0.6–1.2) significant ( $\chi^2 = 2.34$ ;  $p = 0.12$ ). For mortality of those incident cases in risk confined to the low mortality, the risk was high (relative risk, 1.9; 95% confidence interval, 1.1–3.2).

In Table 5-6 we show the relation between cholesterol and colorectal cancer risk estimates were statistically

Because the curves do not suggest an inverse relationship, we suggested several site-specific cancer categories. We categorized sites a posteriori to groups of related cancers. The smoking-related sites, larynx, esophagus, pancreas, and lung (Hoffman 1982; Austin and Cole 1990) were in the same sites as those in melanoma (Hoffman 1982; Austin and

**Table 5-6 Relationship Between Age and Gender According to Gender**

Men	
No. of cases	
Relative risk*	
(95% confidence interval)	
Multivariate relative risk†	
(95% confidence interval)	
Women	
No. of cases	
Relative risk‡	
(95% confidence interval)	
Multivariate relative risk‡	
(95% confidence interval)	

\*Based on proportional hazards model.

‡Model includes variables for age, calories, age at first birth, age at menarche, and model.

was analyzed and when incident cases reported by death certificate only were eliminated.

For incidence of cancer in women, there was a small, nonsignificant increase in risk confined to the lowest quintile of cholesterol (Table 5-5). The multivariate relative risk estimates for incidence in women were 1.2 (0.8-1.9), 1.0 (0.7-1.5), 0.8 (0.6-1.2), and 0.9 (0.6-1.2). The multivariate trend test for incidence was not significant ( $\chi^2 = 2.34$ ;  $p = 0.13$ ). Negligible differences resulted from the elimination of those incident cases identified from death certificate only. In the analysis of mortality, the risk was higher for women in the lowest quintile for cholesterol (relative risk, 1.9; 95% confidence interval, 1.0-3.4).

In Table 5-6 we show more detailed data on the association between serum cholesterol and colorectal cancer. Although there was a suggestion of an inverse relation between cholesterol and colorectal cancer among men, none of the relative risk estimates were statistically significant. No association was seen in women.

Because the curves depicting incidence and the results of regression analyses suggested an inverse relation between concentration of cholesterol in serum and several site-specific cancers known to be related to cigarette smoking, we aggregated sites a posteriori to form categories of smoking-related and non-smoking-related cancers. The smoking-related cancers in men were those of the lung, mouth, larynx, esophagus, pancreas, and bladder and leukemia (Wynder and Hoffman 1982; Austin and Cole 1986). In women the smoking-related cancers were at the same sites as those in men, plus the additional site of the cervix (Wynder and Hoffman 1982; Austin and Cole 1986). Age-adjusted incidence rates for the smok-

**Table 5-6** Relationship Between Level of Serum Cholesterol and Colorectal Cancer According to Gender

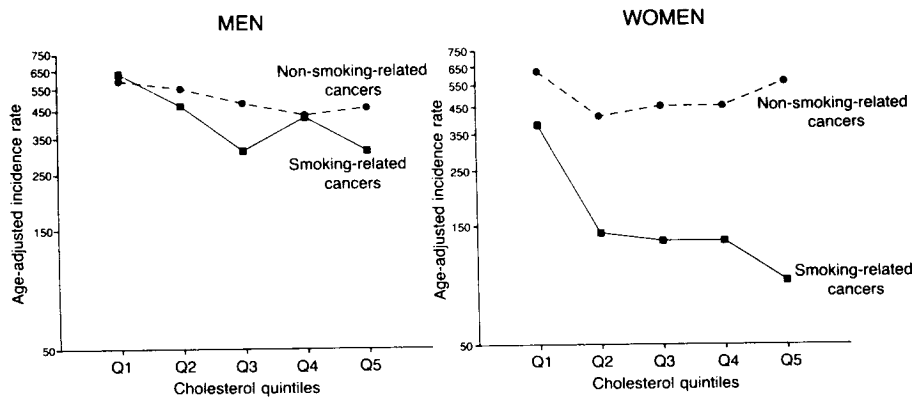
	Cholesterol Quartiles			
	<198	190-216	217-246	>247
<b>Men</b>				
No. of cases	16	18	10	18
Relative risk*	1.3	1.2	0.6	(1.0)
(95% confidence interval)	(0.6-2.5)	(0.6-2.4)	(0.3-1.3)	—
Multivariate relative risk†	1.7	1.2	0.5	(1.0)
(95% confidence interval)	(0.8-3.7)	(0.5-2.6)	(0.2-1.4)	—
	<186	187-217	218-251	>252
<b>Women</b>				
No. of cases	6	13	23	26
Relative risk‡	0.9	1.1	1.2	(1.0)
(95% confidence interval)	(0.4-2.2)	(0.6-2.2)	(0.7-2.2)	—
Multivariate relative risk‡	1.0	0.9	1.3	(1.0)
(95% confidence interval)	(0.3-2.7)	(0.4-2.1)	(0.6-2.4)	—

\*Based on proportional hazards models including variables for age and cholesterol.

†Model includes variables for age, education, body mass index, smoking (pack-years), alcohol, fat as a percentage of calories, dietary fiber, and cholesterol. Forty-five cases were analyzed in the multivariate model.

‡Model includes variables for age, education, body mass index, smoking (pack-years), alcohol, fat as a percentage of calories, age at first birth, age at menarche, parity, and cholesterol. Forty-eight cases were analyzed in the multivariate model.

WITH LITERATURE



**Fig. 5-4.** Age-adjusted incidence of smoking- and non-smoking related cancers according to level of serum cholesterol and gender. The first through fifth quintiles of cholesterol (mg/100 ml) were as follows: for men,  $\leq 182$ , 183–205, 206–226, 227–254,  $\geq 255$ ; for women,  $\leq 179$ , 180–203, 204–229, 230–261,  $\geq 262$ .

ing-related and non-smoking-related cancers by quintiles of cholesterol are displayed in Fig. 5-4.

A definite inverse relation between cholesterol and cancer similar to that seen for all cancer was found for smoking-related cancers, whereas only a weak inverse relation was noted for non-smoking-related cancers. Among women only, an inverse relation was also apparent for smoking-related cancers, but not for non-smoking-related cancers.

Table 5-7 gives the relative risk estimates for smoking-related and non-smoking-related cancers in men in each of the serum cholesterol quintiles. A clear inverse relation was present for smoking-related cancers in men (Table 5-7), with multivariate relative risk estimates of 2.1 (1.1–3.8), 1.6 (0.8–2.9), 1.1 (0.6–2.2), and 1.4 (0.7–2.5) for the first to fourth quintiles. (The highest quintile is the reference group.) The multivariate test for trend was significant ( $p = 0.02$ ). Since the etiologic link between smoking and leukemia is not as well established as that for the other smoking-related cancers mentioned, we performed separate analyses without leukemia in the smoking-related cancers group. The multivariate risk estimates for smoking-related cancers minus leukemia (101 cases) were 2.1 (1.1–4.0), 1.8 (0.9–3.3), 1.1 (0.6–2.2), and 1.3 (0.7–2.4). (Again, the reference group was the highest cholesterol quintile.) The trend test showed a  $p$ -value of  $= 0.01$ . In addition, since the ascertainment of cancer solely by death certificate might have been less accurate than ascertainment by hospital records, we examined the relation between cholesterol and cancer for smoking-related cancers confirmed by hospital records. Estimates of relative risk were not substantially altered. For the non-smoking-related cancers, there was a weak inverse relation, with  $\chi^2 = 3.35$  ( $p = 0.07$ ) for the multivariate trend test.

For women an inverse relation, considerably stronger than the one for all

**Table 5-7** Relationship Between Levels of Serum Cholesterol and the Occurrence of Smoking-related and Nonsmoking-related Cancers for Men

Serum cholesterol level (mg/100ml)		
<182	183–205	206–226
(n = 1008)	(n = 1000)	(n = 1023)
		227–254
		(n = 1065)
		>255
		(n = 1029)

**Table 5-7** Relationship Between Levels of Serum Cholesterol and the Occurrence of Smoking-related and Nonsmoking-related Cancers for Men

Men	Serum cholesterol level (mg/100ml)				
	<182 (n = 1008)	183-205 (n = 1000)	206-226 (n = 1023)	227-254 (n = 1065)	>255 (n = 1029)
Smoking-related cancers					
No. of cases	49	44	32	48	38
Relative risk*	2.0	1.4	0.9	1.3	(1.0)
(95% Confidence interval)	(1.3-3.0)	(0.9-2.2)	(0.6-1.5)	(0.8-2.0)	—
Multivariate relative risk†	2.1	1.6	1.1	1.4	(1.0)
(95% Confidence interval)	(1.1-3.8)	(0.8-2.9)	(0.6-2.2)	(0.7-2.5)	—
Non-smoking-related cancers					
No. of cases	45	51	49	49	54
Relative risk*	1.3	1.2	1.0	0.9	(1.0)
(95% Confidence interval)	(0.8-1.9)	(0.8-1.7)	(0.7-1.5)	(0.7-1.4)	—
Multivariate relative risk†	1.6	1.4	0.9	1.2	(1.0)
(95% Confidence interval)	(0.9-2.7)	(0.9-2.4)	(0.5-1.6)	(0.7-2.0)	—

\*Based on proportional hazards model including variables for age and cholesterol.

†Model includes variables for age, education, body mass index, smoking (pack-years), alcohol, fat as a percentage of calories, dietary fiber, and cholesterol. The total number of cases in the multivariate models for all cancers, smoking-related cancers, and non-smoking-related cancers were, respectively, 261, 112, 149. Multivariate trend tests for the relation of cholesterol to all cancer, smoking-related cancers, and non-smoking-related cancers in men yielded, respectively,  $\chi^2 = 8.83$  ( $p = 0.003$ ),  $\chi^2 = 5.48$  ( $p = 0.02$ ),  $\chi^2 = 3.35$  ( $p = 0.07$ ).

cancer, was evident for the smoking-related cancers, with a multivariate relative risk estimate of 3.3 (1.4–7.8) for the lowest compared to the highest quintile (Table 5–8). The test for trend for smoking-related cancers yielded  $p = 0.02$ . The estimates of relative risk for smoking-related cancers minus leukemia (only 45 cases) were 2.2 (0.8–5.7), 1.2 (0.5–3.2), 0.7 (0.3–1.8), and 0.9 (0.4–2.0) (highest cholesterol quintile as reference), with a multivariate trend test yielding  $\chi^2 = 1.44$  ( $p = 0.23$ ). Relative risk estimates for smoking-related cancers did not differ materially, whether based on hospital records alone or on hospital records combined with death certificates. No association was evident between cholesterol and non-smoking-related cancers in women.

The relation of cholesterol to incidence of all cancers, incidence of smoking-related and non-smoking-related cancer, and mortality due to cancer was similar across subgroups of various risk factors for cancer, including age, education, body mass index, smoking, alcohol consumption, and fat consumption. Among women the inverse relation observed between cholesterol and cancer for incidence of all cancers was restricted to women under the age of 50 years.

Because of concern for residual confounding by smoking, we focused on the relation between cholesterol and smoking-related cancers (not exclusively attributable to smoking) among nonsmokers. For male nonsmokers the relative risk estimates and 95% confidence intervals from the first to the fourth cholesterol quintiles for smoking-related cancers (25 cases) were 4.7 (1.3–17), 2.0 (0.5–8.4), 1.2 (0.2–5.8), and 1.0 (0.2–4.9) (reference was highest cholesterol quintile). The analogous estimates for smoking-related cancers (40 cases) among nonsmoking women were 2.5 (0.8–8.1), 2.2 (0.8–6.3), 2.0 (0.8–5.0), and 1.8 (0.8–4.3).

Finally, to explore the possibility that preclinical cancer was depressing cholesterol levels (the “preclinical cancer effect” hypothesis), we analyzed the relation between cholesterol and cancer within three distinct follow-up periods: 0 to 1.9, 2 to 5.9, and 6 or more years from the measurement of cholesterol measurement to the diagnosis of cancer. For incidence of all cancer, we analyzed only those cases confirmed by hospital records, since the time of cancer diagnosis was thought to be less reliable for cases identified by death certificate only. As Table 5–9 demonstrates, the inverse relation among men was strongest for cases diagnosed 6 or more years after serum cholesterol was determined. For women there was a statistically significant excess risk only among women in the lowest cholesterol quintile in whom cancer was diagnosed within two years of measurement of cholesterol.

As the data in Table 5–10 show, the inverse relation between cholesterol and smoking-related cancers persisted in both men and women for cases that were diagnosed more than 6 years or more than 8 years after measurement of cholesterol. Results were not altered in the analyses of smoking-related cancers confirmed by hospital records or in multivariate models including variables for cholesterol, age, education or poverty index ratio, race, body mass index, smoking, alcohol consumption, dietary fat intake, dietary fiber intake, and, for women, age at first birth, age at menarche, parity, and menopausal status. For the 41 smoking-related cancers in men diagnosed 8 or more years after measurement of cholesterol, the age-adjusted relative risk estimates for the first through fourth quintiles, relative to the

**Table 5-8** Relationship Between Levels of Serum Cholesterol and the Occurrence of Smoking-related and Nonsmoking-related Cancers for Women

Women	Serum cholesterol level (mg/100ml)				
	<179 (n = 1409)	180-203 (n = 1502)	204-229 (n = 1489)	230-261 (n = 1484)	>262 (n = 1479)
Smoking-related cancers					
No. of cases	19	12	16	21	18
Relative risk*	4.1	1.7	1.5	1.4	(1.0)
(95% Confidence interval)	(2.1-8.0)	(0.8-3.6)	(0.8-3.0)	(0.8-2.8)	—
Multivariate relative risk†	3.3	1.7	0.7	1.1	(1.0)
(95% Confidence interval)	(1.4-7.8)	(0.7-4.1)	(0.3-1.9)	(0.5-2.4)	—
Non-smoking-related cancers					
No. of cases	37	44	59	74	98
Relative risk*	1.0	0.9	0.9	0.9	(1.0)
(95% Confidence interval)	(0.7-1.6)	(0.6-1.3)	(0.6-1.2)	(0.7-1.2)	—
Multivariate relative risk†	0.9	0.9	0.8	0.8	(1.0)
(95% Confidence interval)	(0.6-1.5)	(0.6-1.3)	(0.6-1.2)	(0.5-1.2)	—

\*Based on proportional hazards model including variables for age and cholesterol.

†Model includes variables for age, education, body mass index, smoking (pack-years), alcohol, fat as a percentage of calories, dietary fiber, age at first birth, age at menarche, parity, and cholesterol. The total number of cases in the multivariate models for all cancer, smoking-related cancers, and non-smoking-related cancers were 268, 52, 261, respectively. Multivariate trend tests for the relation of cholesterol to all cancer and smoking-related cancers in women yielded  $\chi^2 = 0.34$  ( $p = 0.5$ ), and  $\chi^2 = 5.42$  ( $p = 0.02$ ), respectively.

**Table 5-9** Relationship of Levels of Serum Cholesterol and Relative Risk of Cancer as Confirmed by Hospital Records According to Years of Follow-up and Gender

Serum cholesterol level (mg/100ml)	Relative risk (95% confidence interval) after indicated years of follow-up		
	Zero-1.9	2-5.9	≥6
<b>Men (no. of cases)</b>	56	134	168
≤182	0.8 (0.3-1.9)	1.5 (0.9-2.5)	2.2 (1.3-3.7)
183-205	1.3 (0.6-2.6)	1.0 (0.6-1.7)	1.8 (1.1-3.1)
206-226	0.6 (0.2-1.4)	0.9 (0.6-1.6)	1.7 (1.0-2.9)
227-254	0.8 (0.4-1.7)	0.8 (0.7-2.0)	1.8 (1.1-3.0)
≥255	(1.0) —	(1.0) —	(1.0) —
<b>Women (no. of cases)</b>	58	125	153
≤179	3.3 (1.3-8.2)	0.6 (0.3-1.3)	1.0 (0.6-1.8)
180-203	1.3 (0.4-3.8)	1.0 (0.6-1.8)	0.8 (0.5-1.4)
204-229	2.8 (1.5-5.9)	0.8 (0.5-1.3)	0.7 (0.4-1.2)
230-261	1.9 (0.9-4.0)	0.6 (0.4-1.0)	1.0 (0.7-1.5)
≥262	(1.0) —	(1.0) —	(1.0) —

Note: Age-adjusted relative risks and 95% confidence intervals were derived from follow-up time-specific proportional hazards models that included variables for age and cholesterol. Estimates were only minimally altered in multivariate models that included variables for age, cholesterol, education, body mass index, smoking (pack-years), alcohol, dietary fat as a percentage of total calories, dietary fiber, and, for women, age at first birth, age at menarche, and parity.

highest quintile, were 5.9 (2.0-18), 1.5 (0.4-5.5), 2.2 (0.7-7.2), and 2.2 (0.7-7.2). (There were only 17 such cases in women.)

### Discussion

Our analysis of the relation between serum cholesterol level and cancer in men confirmed the inverse association that has been reported in numerous cohort studies. There was at most, however, a small, nonsignificant inverse relation for colorectal cancer. The inverse relation was somewhat stronger for smoking-related as opposed to non-smoking-related cancers, with a doubling in risk of smoking-related cancer among men in the lowest cholesterol quintile. The inverse relation for incidence of all cancer and of smoking-related cancers persisted for several years after cholesterol was measured (Schatzkin et al. 1987, 1988).

Among women we found a nonsignificant inverse relation between serum cholesterol level and incidence of cancer that was restricted to women in the lowest cholesterol quintile. For mortality attributable to cancer, however, the inverse relation (again confined to the lowest quintile) was considerably stronger. There was also a strong inverse association of cholesterol level with smoking-related cancers in women but no association with the non-smoking-related cancers. The findings for smoking-related and non-smoking-related cancers are compatible with results of the analysis of mortality, in that the mortality experience associated with smoking-related cancers in women tends to be less favorable than that associated with non-smoking-related cancers (e.g., cancer of the breast and uterine corpus) (Sondik et al. 1986). The inverse relation seen for all cancer in women was confined largely to

**Table 5-10** Relationships of Serum Cholesterol Level and Relative Risk of Cancer

Serum cholesterol level (mg/100ml)
<b>Men (no. of cases)</b>
≤182
183-205
206-226
227-254
≥255
<b>Women (no. of cases)</b>
≤179
180-203
204-229
230-261
≥262

Note: Relative risks (95% confidence intervals) were derived from follow-up time-specific proportional hazards models that included variables for age and cholesterol. Although estimates were only minimally altered in multivariate models that included variables for age, cholesterol, education, body mass index, smoking (pack-years), alcohol, dietary fat as a percentage of total calories, dietary fiber, and, for women, age at first birth, age at menarche, and parity.

the first 2 years of follow-up. The relation persisted over several years after cholesterol was measured.

The "preclinical" cancer hypothesis, which suggests that the relation between cholesterol and cancer is mediated by the effect of cholesterol on the development of preclinical cancer, is supported by the finding that the relation between cholesterol and cancer is stronger for smoking-related cancers than for non-smoking-related cancers. The finding that the relation between cholesterol and cancer is stronger for smoking-related cancers than for non-smoking-related cancers is also consistent with the finding that the relation between cholesterol and cancer is stronger for smoking-related cancers than for non-smoking-related cancers. The finding that the relation between cholesterol and cancer is stronger for smoking-related cancers than for non-smoking-related cancers is also consistent with the finding that the relation between cholesterol and cancer is stronger for smoking-related cancers than for non-smoking-related cancers.

Finally, if smoking-related cancers are more common to those anatomic sites that are more susceptible to smoke, and if these pro-

**Table 5-10** Relationship of Levels of Serum Cholesterol and Relative Risk of Smoking-related Cancers According to Years of Follow-up and Gender

Serum cholesterol level (mg/100ml)	Relative risk (95% confidence interval) after indicated years of follow-up		
	0-1.9	2-5.9	≥6
<b>Men (no. of cases)</b>	32	90	80
≤182	1.3 (0.4-4.2)	1.7 (0.9-5.1)	2.5 (1.3-4.9)
183-205	1.9 (0.7-2.5)	1.3 (0.7-2.5)	1.4 (0.7-2.8)
206-226	0.4 (0.1-2.0)	0.9 (0.5-1.9)	1.2 (0.6-2.4)
227-254	1.7 (0.6-4.8)	1.0 (0.5-1.9)	1.5 (0.7-2.9)
≥255	(1.0) —	(1.0) —	(1.0) —
<b>Women (no. of cases)</b>	15	38	33
≤179	8.8 (1.5-49)	1.8 (0.6-5.6)	6.2 (2.1-18)
180-203	3.0 (0.4-22)	1.7 (0.6-4.6)	1.3 (0.3-5.3)
204-229	1.8 (0.3-13)	1.1 (0.4-3.0)	2.0 (0.7-6.1)
230-261	3.2 (0.6-17)	1.1 (0.5-2.8)	1.5 (0.5-4.5)
≥262	(1.0) —	(1.0) —	(1.0) —

Note: Relative risks (95% confidence intervals) were derived from proportional hazards models that included variables for age and cholesterol. Although the multivariate models were relatively unstable due to the small number of cases, estimates were only minimally altered in models that included variables for age, cholesterol, education, body mass index, smoking (pack-years), alcohol, dietary fat as a percentage of total calories, dietary fiber, and, for women, age at first birth, age at menarche, and parity.

the first 2 years of follow-up, but for the smoking-related cancers the inverse relation persisted over a longer period of follow-up.

The "preclinical cancer effect" hypothesis for the observed inverse relation between cholesterol and cancer is an attractive explanation given the protean physiologic manifestations of malignant disease, which could well include depression of serum cholesterol levels. In that regard, it has long been known that patients with leukemia have reduced cholesterol levels (Muller 1930), and it has recently been shown that leukemic cells have an elevated low-density lipoprotein receptor activity that is inversely correlated with plasma cholesterol levels (Vitols et al. 1985). We found, however, that the inverse relation between cholesterol and all incident cancer in men held for several years after cholesterol was measured. For smoking-related cancers this relation held for women as well as for men. Although one cannot totally exclude the possibility that nascent neoplasms could alter cholesterol metabolism several years prior to clinical diagnosis, our findings and those from a few other studies (Beaglehole et al. 1980; Garcia-Palmieri et al. 1981; Kark, Smith, and Hames 1980; Peterson and Trell 1983; Sorlie and Feinleib 1982) suggest that there is more to the inverse relation between cholesterol and cancer than a short-term effect of preclinical cancer. We note also that the inverse relation between cholesterol and leukemia obtained even after exclusion of cases diagnosed within the first 2 years after determinations of cholesterol levels.

Finally, if smoking-related cancers stemmed from pathologic processes common to those anatomic sites most susceptible to the carcinogenic effects of tobacco smoke, and if these processes were linked with depression of the serum cholesterol

level, then the inverse relation between cholesterol and smoking-related cancers would be found. However, it is unclear whether a low level of cholesterol is a necessary precondition for such processes or merely an incidental effect. If the latter were true, then the explicit reduction of serum cholesterol for prevention of coronary disease would not in itself increase the risk of cancer. We emphasize that our aggregation of cancer sites into smoking-related and non-smoking-related cancers was not driven by a prior hypothesis. Inferences drawn from this kind of post hoc grouping must be considered cautiously, and our finding for smoking-related cancers needs to be examined with other sets of data.

Although we cannot now offer more than a very general explanation for the observed inverse relation between cholesterol and cancer, we conclude that the findings are strong enough to merit continued epidemiologic investigation.

#### SOCIOECONOMIC STATUS AND CANCER

The relation between two sociodemographic variables, education and income, and cancer (incidence and mortality for cancer at all sites, and incidence at major sites) is the subject of our fourth investigation of the epidemiology of cancer, utilizing the NHEFS data set. Since the NHEFS cohort was derived from a probability sample of the U.S. population, accompanied by oversampling of groups hypothesized to be at increased risk of nutritional deprivation, there is a considerable spread of educational achievement and income across the cohort.

Previous studies have shown higher rates of total malignant disease among those at the lower end of the socioeconomic scale (American Cancer Society 1986; Kitagawa and Hauser 1973; Logan 1982). For several cancer sites, including lung (Devesa and Diamond 1983), cervix (Brinton and Fraumeni 1986), esophagus (Day 1975), and stomach (Haenszel and Correa 1975), inverse relations with socioeconomic status have generally been reported. However, consistent trends across social classes have not been demonstrated for colorectal (Schottenfeld and Winawer 1982) or prostate (Mandel and Schuman 1979) cancer. Although a positive association between socioeconomic status and breast cancer has been found (Kelsey 1979), the magnitude of this relation is not great and may be diminishing over time (Logan 1982).

#### Analytic Methodology

The cohorts used in the analyses of education and income in relation to cancer were similar to those analyzed in the study of the cholesterol-cancer association. Baseline data on education were missing for 54 men and 51 women, whereas baseline data on income were missing for 225 men and 322 women.

The analyses of education and incident cancer included 5100 men and 7374 women; those for income and cancer included 4952 men and 7146 women. The comparable analyses for mortality due to cancer involved 5757 men and 8545 women for education, 5586 men and 8274 women for income.

Smoking-related and manner as in the study of

#### Observed Correlations b

Classification of the cohort indicated that a substantial proportion with 33% of the men and high school. Only 21% of the high school. At least some of the men and 60% of the women reported less and 19% of the women reported men and women (58% and \$4000-9999).

Data reflecting the and other potential risk factors instances, the associations income. Low socioeconomic associated with being older and energy) and less fiber, and, menarche, and greater parity index, was inversely related education in men, but there among men. A greater socioeconomic status reported association between total living levels for women were largely unrelated to education and women in higher, as reported being former smokers serum cholesterol and education income and cholesterol level cholesterol level and education, income. The proportion of with more education and education was positively associated there was a strong direct association

Figures 5-5 and 5-6 cancer by level of education socioeconomic status level and non-smoking-related cancer

Men of lower socioeconomic inverse trend being somewhat association appeared large

Smoking-related and non-smoking-related cancers were defined in the same manner as in the study of the association between cholesterol and cancer.

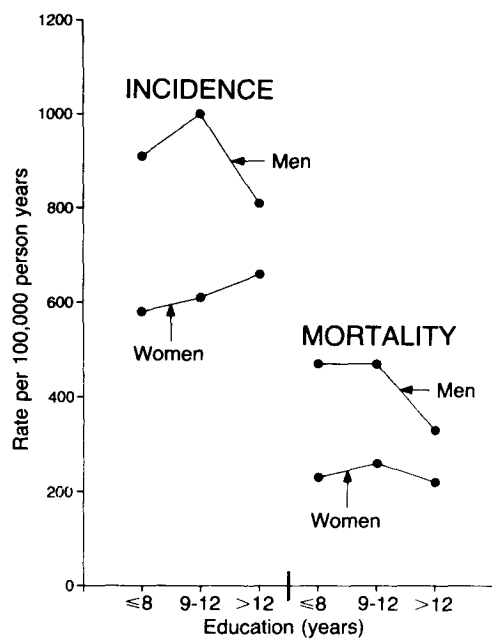
#### Observed Correlations between Socioeconomic Status and Cancer

Classification of the cohorts studied by broad education and income groups indicated that a substantial proportion of subjects had relatively little formal education, with 33% of the men and 23% of the women completing no more than elementary school. Only 21% of the men and 17% of the women had any education beyond high school. At least some schooling in grades 9 through 12 was reported by 46% of the men and 60% of the women. With regard to income, 20% of the men and 24% of the women reported less than \$4000 per year, whereas only about 22% of the men and 19% of the women received \$10,000 or more annually. Similar proportions of men and women (58% and 57%, respectively) had annual incomes in the mid-range (\$4000-9999).

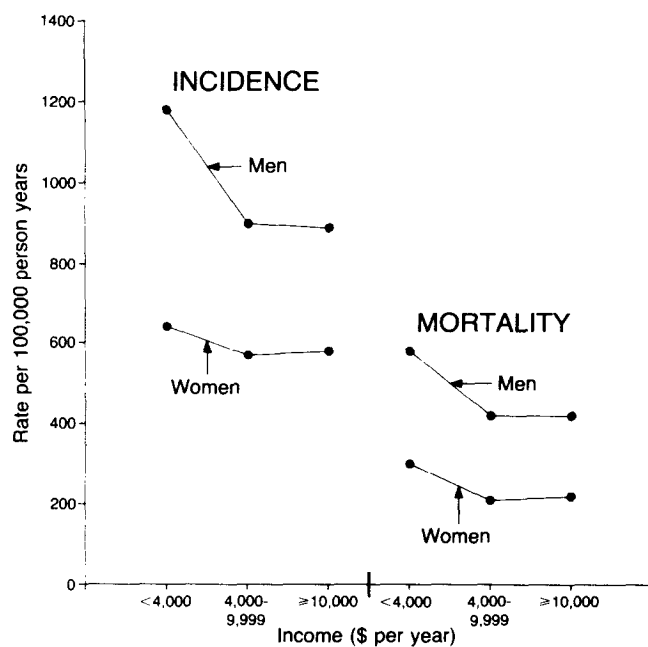
Data reflecting the relations between the two socioeconomic status variables and other potential risk factors for cancer can be summarized as follows. In most instances, the associations with other risk factors were similar for education and income. Low socioeconomic status and educational achievement tended to be associated with being older and nonwhite, consuming more fat (as a percentage of total energy) and less fiber, and, in women, having an earlier age at first birth, later age at menarche, and greater parity. Among women, obesity, as reflected by body mass index, was inversely related to both education and income and, to a lesser degree, to education in men, but there was a slight positive association of obesity with income among men. A greater proportion of men with lower, as opposed to higher, socioeconomic status reported being current smokers, but among men there was little association between total pack-years of smoking and socioeconomic status. Smoking levels for women were generally lower than those for men, and they were largely unrelated to education and slightly inversely related to income. (More men and women in higher, as compared with lower, education and income brackets reported being former smokers.) Among men there was no association between serum cholesterol and education, but there was a small inverse association between income and cholesterol level. Data for women showed a positive relation for cholesterol level and education, with little apparent relation between cholesterol level and income. The proportion of menopausal women was slightly higher among those with more education and income. Among both men and women, alcohol consumption was positively associated with socioeconomic status. As one would expect, there was a strong direct association between educational achievement and income.

Figures 5-5 and 5-6 depict age-adjusted incidence and mortality rates for all cancer by level of education and income. Figures 5-7 through 5-10 display the socioeconomic status level-specific rates for major cancer sites and for the smoking- and non-smoking-related cancers.

Men of lower socioeconomic status had higher overall rates of cancer, with the inverse trend being somewhat stronger for mortality than for incidence. This inverse association appeared largely among the smoking-related, as opposed to non--

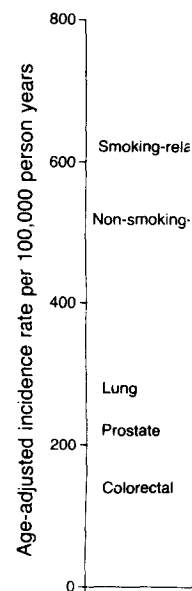


**Fig. 5-5.** Age-adjusted cancer incidence and mortality rates (per 100,000 persons-years) according to education and gender.



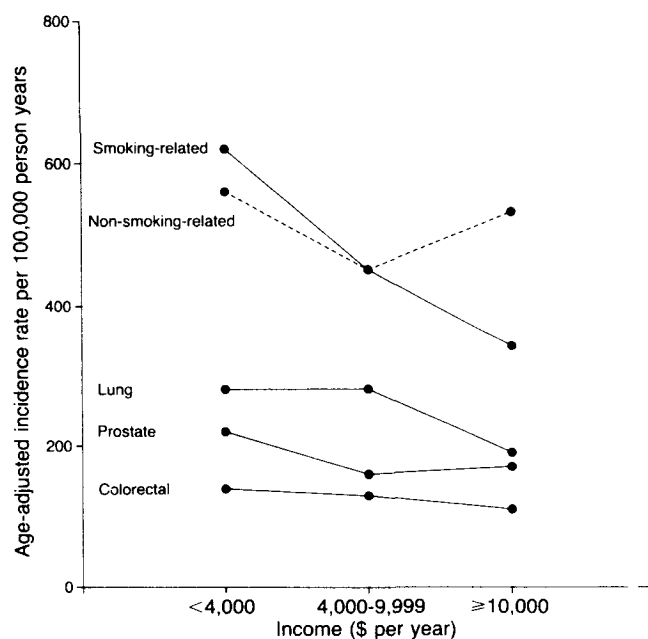
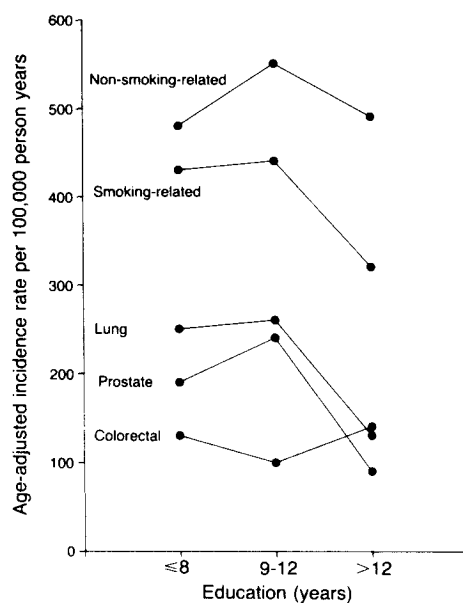
**Fig. 5-6.** Age-adjusted cancer incidence and mortality rates (per 100,000 person-years) according to income and gender.

**Fig. 5-7.** Age-adjusted incidence rates (per 100,000 person-years) for prostate, colorectal, and lung cancer, and non-smoking-related cancer, according to level of education.

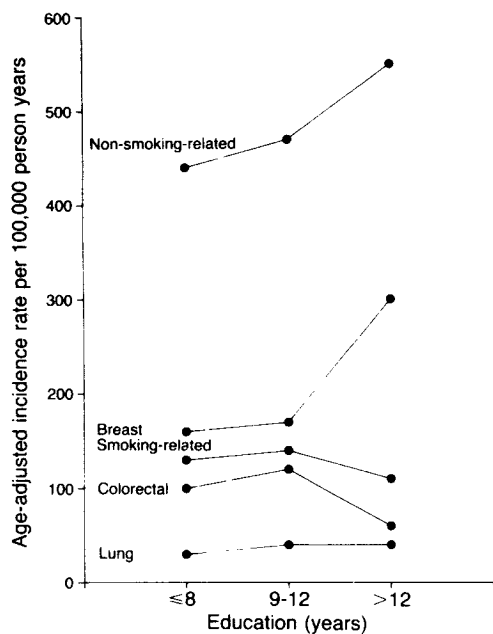


**Fig. 5-8.** Age-adjusted incidence rates (per 100,000 person-years) for prostate, colorectal, and lung cancer, and non-smoking-related cancer, according to level of education.

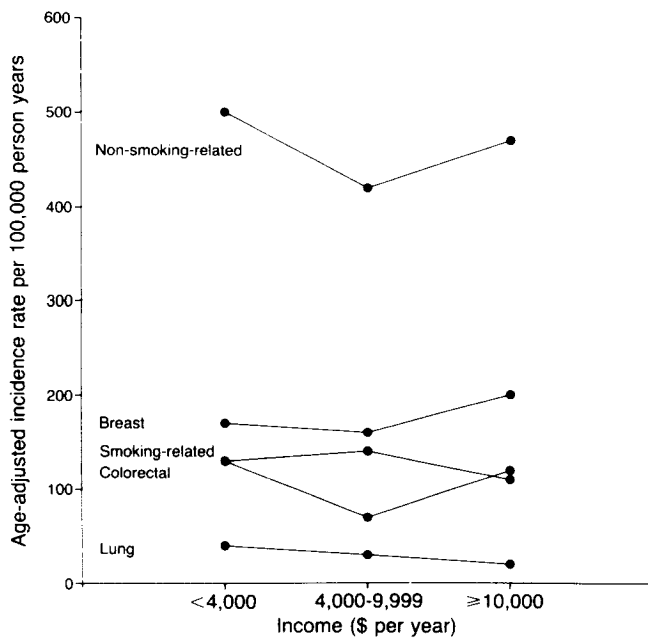
**Fig. 5-7.** Age-adjusted incidence (per 100,000 person-years) of lung, prostate, colorectal, and smoking- and non-smoking-related cancers according to level of education for men.



**Fig. 5-8.** Age-adjusted incidence (per 100,000 person-years) of lung, prostate, colorectal, and smoking- and non-smoking-related cancers according to level of income for men.



**Fig. 5-9.** Age-adjusted incidence (per 100,000 person-years) of lung, breast, colorectal, and smoking- and non-smoking-related cancers according to level of education for women.



**Fig. 5-10.** Age-adjusted incidence (per 100,000 person-years) of lung, breast, colorectal, and smoking- and non-smoking-related cancers according to level of income for women.

## CANCER / 103

**Table 5-11** Rates of Cancer Education, Gender and Age at

	<55 Yr	
	<8	9
Men		
All cancer incidence	530	2
All cancer mortality	350	1
Smoking cancer incidence	280	1
Nonsmoking cancer incidence	250	1
Women		
All cancer incidence	300	2
All cancer mortality	850	8
Smoking cancer incidence	70	
Nonsmoking cancer incidence	240	2

smoking-related, cancers. Men had higher rates of lung cancer than women. There was at most a slight inverse trend for socioeconomic status, whereas for education and a slight inverse trend for income.

Since a deterioration in health status with increasing income (Luft 1978), we examined the elimination of the first two periods. The rates were not materially different from those for the entire period.

The relation between socioeconomic status and cancer incidence was different. Incidence of cancer was higher among men than among women, as there was no consistent trend for income. There was a small inverse trend for income for men. Smoking-related cancers, all cancers in women than in men, and all cancers with socioeconomic status. The association was observed between socioeconomic status, but the association was not observed between cancer. As among men, there was no association between income and colorectal cancer.

Age-specific cancer rates for men and women showed the inverse relations appeared for men and women, inverse socioeconomic status for men aged under 55 and 65 years. For women, positive for women aged 55-

**Table 5-11** Rates of Cancer (per 10,000 person years) According to Years of Education, Gender and Age at Baseline (NHANES I)

	Indicated age groups and years of education								
	<55 Years of age			55-64 Years of age			>65 Years of age		
	<8	9-12	>12	<8	9-12	>12	<8	9-12	>12
<b>Men</b>									
All cancer incidence	530	280	210	1210	1320	1220	2280	2550	2060
All cancer mortality	350	140	70	680	610	680	1080	1250	800
Smoking cancer incidence	280	150	70	600	440	600	1030	1180	800
Nonsmoking cancer incidence	250	130	140	610	870	610	1230	1350	1250
<b>Women</b>									
All cancer incidence	300	260	250	560	760	1400	1340	1420	1260
All cancer mortality	850	840	600	240	400	540	620	650	440
Smoking cancer incidence	70	50	40	130	100	280	270	410	200
Nonsmoking cancer incidence	240	210	230	480	600	960	990	1080	1100

smoking-related, cancers. Men with lower educational achievement and income had higher rates of lung cancer than their male counterparts with higher socioeconomic status. There was at most a small inverse relation between prostate cancer and socioeconomic status, whereas for colorectal cancer there was no association for education and a slight inverse relation for income.

Since a deterioration in health status before diagnosis of cancer might lower income (Luft 1978), we examined the relation between income and cancer after elimination of the first two person-years of follow-up. The income-cancer relations were not materially different from those described earlier.

The relation between socioeconomic status and cancer among women was different. Incidence of cancer showed a small positive relation to education, whereas there was no consistent trend for income. For mortality due to cancer, there was a small inverse trend for income and an even smaller inverse association for education. Smoking-related cancers, which made up a considerably smaller proportion of all cancers in women than in men, demonstrated only a small inverse association with socioeconomic status. There was no trend for lung cancer in relation to socioeconomic status, but the number of cases in women was quite small. A positive association was observed between both socioeconomic status variables and breast cancer. As among men, there was no clear relation among women between education or income and colorectal cancer.

Age-specific cancer rates are presented in Tables 5-11 and 5-12. Among men the inverse relations appeared to be more prominent for younger subjects. Among women, inverse socioeconomic status-cancer relations were evident for groups aged under 55 and 65 years and older groups; however, the associations were positive for women aged 55-64 years. These age-specific patterns need to be

**Table 5-12** Rates of Cancer (per 10,000 person years) According to Income, Gender, and Age at Baseline (NHANES I)

	Cancer rates for indicated age groups and income level									
	<55 Years of age			55-64 Years of age			>65 Years of age			
	<\$4000	4-9999	>10,000	<4,000	4-9999	>10,000	<4000	4-9999	>10,000	
<b>Men</b>										
All cancer incidence	780	310	280	1740	1190	1240	2330	2250	2480	
All cancer mortality	470	140	100	1070	470	670	1020	1120	1170	
Smoking cancer incidence	600	140	70	960	500	490	860	1200	1040	
Nonsmoking cancer incidence	200	170	146	780	670	740	1440	1030	1410	
<b>Women</b>										
All cancer incidence	280	270	250	760	500	1130	1460	1320	1180	
All cancer mortality	1230	890	630	440	240	470	720	520	490	
Smoking cancer incidence	70	50	40	130	100	280	270	410	200	
Nonsmoking cancer incidence	200	230	210	620	400	850	1190	910	980	

viewed cautiously, however, because of the specific and socioeconomic factors involved.

In Tables 5-13 and 5-14, we present regression analyses of the relationship between cancer incidence and education from models that also included age, race, and income, as discussed earlier. Men with less than a high school education who had some education had a relative risk estimate of 1.5 for men with incomes of \$4000 or less, somewhat greater, with a relative risk of 1.8 for the least versus the most educated, versus the \$3000 as compared with the \$10,000 or more.

Inclusion of smoking status in the regression estimates considerably reduced these estimates.

For women the relative risk for the category of education from 1.0 and did not change. Mortality due to cancer was, however, a marginally significant factor, with a relative risk of 1.5 for those with less than \$4000, compared with those with \$4000 or more, after adjustment for smoking.

## Discussion

Our analyses have shown that cancer incidence is reflected by education, with at most a 50% increase in mortality, greater for men than for women. The relative risk of mortality as compared with cancer among those in the lowest income and income for men and women was similar to the risks observed in relative risk studies. The association between education and cancer incidence appeared after adjustment for income.

Studies of socioeconomic status and cancer tend to lack specificity. "biologic" exposures are often used as surrogates for education, but they may be surrogates for education, but they may be surrogates for education. The variation in cancer incidence across income-related factors is often small, and the variation in cancer incidence across income-related factors is often small.

viewed cautiously, however, because the numbers of cases within each of the age-specific and socioeconomic status-specific categories were rather small.

In Tables 5-13 and 5-14 we present results from proportional hazards regression analyses of the relation between the two socioeconomic status variables and all cancer incidence and mortality. The relative risk estimates for education and income from models that also include only age paralleled the age-adjusted incidences discussed earlier. Men who had 12 or fewer years of schooling, as compared with those who had some education past high school, had approximately a 10-20% greater risk of cancer. In comparison with those who had incomes of \$10,000 or more, the relative risk estimate for incidence was 1.3 (95% confidence interval 1.0-1.6) for men with incomes of less than \$4000. The excess risk of mortality among men was somewhat greater, with marginally significant point estimates of 1.4 (1.0-2.1) for the least versus the most educated, and 1.6 (1.0-2.3) for an income of less than \$3000 as compared with \$10,000 or more.

Inclusion of smoking as well as age in the models for men lowered these point estimates considerably. Inclusion of multiple risk factors in the regression models reduced these estimates to or very near 1.0.

For women the age-adjusted point estimates of cancer incidence for the lowest category of education and income, relative to the highest, were negligibly different from 1.0 and did not change with adjustment for smoking and other risk factors. For mortality due to cancer, risk was at most minimally increased with education. There was, however, a marginally significant excess risk for those with incomes of less than \$4000, compared with \$10,000 or more. This effect did not diminish after adjustment for smoking and other risk factors.

## Discussion

Our analyses have shown that the inverse relation between socioeconomic status, as reflected by educational achievement or income, and cancer was of modest dimension, with at most a 50% excess risk. Overall the inverse association was somewhat greater for men than for women, for younger than for older subjects, and for cancer mortality as compared with cancer incidence. The increased risk of death due to cancer among those in the lowest, as opposed to highest, brackets of both education and income for men and of income for women was approximately 50%. The excess risks observed in relation to socioeconomic status, with the exception of a persistent association between income and mortality due to cancer in women, largely disappeared after adjustment for smoking and other risk factors for cancer.

Studies of socioeconomic status and cancer (or any disease, for that matter) tend to lack specificity in the sense that particular (and potentially modifiable) "biologic" exposures are not investigated. Education and income are considered to be surrogates for elements of the sociophysical environment that have a causal relation to disease. That is, it is not the differences in income itself that account for the variation in cancer rates, but the differences in smoking, diet, or some unmeasured factors across the different income groups that govern the corresponding income-related differences in frequency of cancer.

Table 5-13 Relationship Between Education and Income and Cancer Incidence and Mortality for Men

Variable	Age-adjusted		Age-smoking-adjusted		Multiple risk factor adjusted*	
	Relative risk	95% Confidence interval	Relative risk	95% Confidence interval	Relative risk	95% Confidence interval
<i>All cancer incidence</i>						
Education						
≤8	1.1	(0.6-1.5)	1.0	(0.7-1.4)	1.0	(0.7-1.4)
9-12	1.2	(0.9-1.6)	1.0	(0.7-1.4)	1.0	(0.7-1.4)
≥12	(1.0)	—	(1.0)	—	(1.0)	—
Income						
<\$4000	1.3	(1.0-1.6)	1.1	(0.8-1.5)	1.1	(0.8-1.6)
4001-9999	1.1	(0.8-1.4)	1.0	(0.8-1.3)	1.0	(0.8-1.3)
≥10,000	(1.0)	—	(1.0)	—	(1.0)	—
<i>All cancer mortality</i>						
Education						
≤8	1.4	(1.0-2.1)	1.2	(0.8-1.8)	1.0	(0.7-1.4)
9-12	1.4	(1.0-2.1)	1.1	(0.7-1.6)	1.0	(0.7-1.4)
≥12	(1.0)	—	(1.0)	—	(1.0)	—
Income						
<\$4000	1.6	(1.0-2.3)	1.2	(0.8-1.8)	1.1	(0.8-1.6)
4001-9999	1.1	(0.7-1.6)	1.0	(0.7-1.4)	1.0	(0.8-1.3)
≥10,000	(1.0)	—	(1.0)	—	(1.0)	—
<i>Incidence of smoking-related cancers</i>						
Education						
≤8	1.4	(0.9-2.1)	1.1	(0.7-1.8)	1.2	(0.7-1.9)
9-12	1.3	(0.9-2.1)	1.0	(0.6-1.6)	1.0	(0.6-1.6)
≥12	(1.0)	—	(1.0)	—	(1.0)	—
Income						
<\$4000	1.5	(1.0-2.3)	1.4	(0.9-2.3)	1.4	(0.9-2.3)
4001-9999	1.5	(1.0-2.1)	1.4	(0.9-2.1)	1.4	(1.0-2.2)
≥10,000	(1.0)	—	(1.0)	—	(1.0)	—

\*Model includes age, race, smoking (pack-years), body mass index, and alcohol along with education or income (all entered as indicators).

Table 5-14 Relationship Between Education and Income and Cancer Incidence and Mortality for Women

Variable	Age-adjusted		Age-smoking-adjusted		Multiple risk factor adjusted*	
	Relative risk	95% Confidence interval	Relative risk	95% Confidence interval	Relative risk	95% Confidence interval
<i>All cancer incidence</i>						
Education						
≤8	0.9	(0.7-1.2)	0.8	(0.6-1.1)	0.9	(0.6-1.2)
9-12	0.9	(0.7-1.2)	0.9	(0.9-1.2)	0.8	(0.9-1.1)
≥12	(1.0)	—	(1.0)	—	(1.0)	—
Income						
<\$4000	1.1	(0.8-1.4)	1.1	(0.8-1.5)	1.3	(0.9-1.8)

**Table 5-14** Relationship Between Education and Income and Cancer Incidence and Mortality for Women

Variable	Age-adjusted		Age-smoking-adjusted		Multiple risk factor adjusted*	
	Relative risk	95% Confidence interval	Relative risk	95% Confidence interval	Relative risk	95% Confidence interval
<i>All cancer incidence</i>						
Education						
≤8	0.9	(0.7-1.2)	0.8	(0.6-1.1)	0.9	(0.6-1.2)
9-12	0.9	(0.7-1.2)	0.9	(0.9-1.2)	0.8	(0.9-1.1)
≥12	(1.0)	—	(1.0)	—	(1.0)	—
Income						
<\$4000	1.1	(0.8-1.4)	1.1	(0.8-1.5)	1.3	(0.9-1.8)
4001-9999	0.9	(0.8-1.2)	0.9	(0.7-1.2)	1.0	(0.7-1.3)
≥10,000	(1.0)	—	(1.0)	—	(1.0)	—
<i>All cancer mortality</i>						
Education						
≤8	1.1	(0.7-1.7)	1.1	(0.7-1.8)	1.0	(0.6-1.8)
9-12	1.2	(0.8-1.9)	1.3	(0.8-2.0)	1.1	(0.7-1.9)
≥12	(1.0)	—	(1.0)	—	(1.0)	—
Income						
<\$4000	1.6	(1.0-2.3)	1.6	(1.0-2.4)	1.7	(1.0-3.0)
4001-9999	1.1	(0.7-1.6)	1.1	(0.7-1.7)	1.2	(0.7-1.9)
≥10,000	(1.0)	—	(1.0)	—	(1.0)	—
<i>Incidence of smoking-related cancers</i>						
Education						
≤8	1.3	(0.7-2.5)	1.3	(0.6-2.6)	1.4	(0.6-3.2)
9-12	1.3	(0.7-2.5)	1.1	(0.6-2.3)	0.9	(0.4-1.9)
≥12	(1.0)	—	(1.0)	—	(1.0)	—
Income						
<\$4000	1.0	(0.6-1.9)	1.1	(0.6-2.2)	0.9	(0.4-2.0)
4001-9999	1.2	(0.7-2.2)	1.2	(0.7-2.3)	1.0	(0.5-2.0)
≥10,000	(1.0)	—	(1.0)	—	(1.0)	—

\*Model includes age, race, smoking (pack-years), body mass index, alcohol, age at first birth, parity, age at menarche and age at menopause (all entered as indicators).

Our results clearly show that risk factors for cancer vary markedly with both education and income. Moreover, the results of the multiple regression analyses suggest that known risk factors for cancer, especially smoking, are largely responsible for the inverse relations between socioeconomic status and cancer. In other words, the data suggest that much of the excess cancer observed among men in the lower education and income groups would be eliminated if those men did not smoke more than men in the highest socioeconomic status groups.

Except for the link between income and cancer mortality, there was little relation between socioeconomic status and cancer in women. This finding may reflect the facts that breast cancer, the leading incident cancer in women, had a positive relation with both education and income and that smoking-related cancers (which showed an inverse relation between socioeconomic status and cancer in men) accounted for a substantially smaller proportion of the total cases of cancers in women than in men. The inverse association between income and mortality due to cancer among women that persisted even after adjustment for multiple risk factors suggests that the income variable in women actually may have been a surrogate for other risk factors not included in the regression models. Since mortality reflects survival as well as incidence, it is conceivable that income-related differences in cancer mortality reflect differences in some factors related to survival of women who have cancer.

Although the elevation in cancer risk among those of lower socioeconomic status was small, even a 20–30% increase in risk would have etiologic and public health importance. Where known risk factors can account for socioeconomic differences in cancer rates, it follows that elimination or modification of these factors, such as smoking, could go a long way toward eliminating those differences. It is plausible, although by no means assured, that a reduction in socioeconomic status disparities would be accompanied by a comparable reduction in differential exposure to cancer risk factor across socioeconomic status groups. Finally, the existence of socioeconomic differences in cancer rates not adequately explained by known risk factors suggests the need for discovering other cancer-related factors that vary across categories of socioeconomic status.

#### POSSIBILITIES FOR FUTURE RESEARCH

Some of the cancer studies using the NHEFS data that are presently under way at the National Cancer Institute illustrate additional possibilities for research offered by this data set. Again, it is important to note that NHEFS is an ongoing study. Although the number of cases of cancer at certain sites is rather small for detailed analysis, more cases will accrue in the coming years. Therefore, certain studies of site-specific cancer that are not now possible will become so over the next decade. Moreover, particular hypotheses, such as those relating consumption of alcohol and fat to breast cancer, can be reexamined as additional cases develop in the original NHANES I cohort.

There is considerable interest in the growth to cancer at different sites. Part of NHANES I have included data on obesity and measures of fatness at interview, including those re-examined when examined in a case-control study.

Many research questions remain from both the baseline and follow-up studies concerning cancer in relation to risk factors. These data were collected in a baseline survey.

Information on dietary intake, large bowel and other sites. In carcinogenesis, we have information on fat and fiber in relation to breast cancer. Chemical factors (serum retinol) are correlated with the incidence of cancer.

These samples of ongoing data in epidemiologic investigations.

#### REFERENCES

- American Cancer Society. 1980. "Cancer Facts and Figures." American Cancer Society, New York.
- Armstrong, B., and R. Doll. 1978. "The effect of body-build on mortality in different countries." *British Medical Journal* 15:617–631.
- Austin, H., and P. Cole. 1986. "Cancer in New Zealand." *Journal of the Royal Society of Medicine* 421.
- Begg, C. B., A. M. Walker, and J. M. Walker. 1980. "Breast cancer" (letter). *British Medical Journal* 1:100.
- Beaglehole, R., M. A. Foulkes, and J. M. Walker. 1980. "Cancer in New Zealand Maoris." *British Medical Journal* 1:100.
- Block, G. 1982. "A review of the literature on diet and cancer." *Journal of the National Cancer Institute* 115:492–505.
- Braitman, L. E., E. V. Adlin, and J. M. Walker. 1980. "Cancer in New Zealand Maoris." *British Medical Journal* 1:100.
- Brinton, L. A., and J. F. Fraumeni, Jr. 1980. "Cancer in New Zealand Maoris." *British Medical Journal* 1:100.
- Byers, T., and D. P. Funch. 1980. "Cancer in New Zealand Maoris." *British Medical Journal* 1:100.
- Cambien, F., P. Ducimitiere, and J. M. Walker. 1980. "Cancer in New Zealand Maoris." *British Medical Journal* 1:100.
- Carroll, K. K. 1980. "Lipids and cancer." *Journal of the National Cancer Institute* 115:492–505.

There is considerable interest in the relation of various indexes of body size and growth to cancer at different sites. The extensive anthropometric data gathered as part of NHANES I have permitted current evaluations of the relation between obesity and measures of frame size to breast cancer. Questions from the NHEFS interview, including those relating to body weight at different ages, may be valuable when examined in a case-control context, especially as the number of available cases increases.

Many research questions remain to be explored with data on dietary factors, from both the baseline and follow-up examinations. Investigators are now examining cancer in relation to reported patterns of consumption of the various food groups. These data were compiled from 24-hour diet recall queries included in the baseline survey.

Information on dietary calcium is being examined in relation to cancer of the large bowel and other sites. Since it is likely that nutrient interactions are important in carcinogenesis, we have begun to look at various combinations of dietary lipids and fiber in relation to breast cancer. In addition to serum cholesterol, other biochemical factors (serum retinol, for example) can be investigated in terms of their correlation with the incidence of cancer.

These samples of ongoing studies illustrate the potential role of the NHEFS data in epidemiologic investigations of the etiology of malignant disease.

## REFERENCES

- American Cancer Society. 1986. *Cancer in the Economically Disadvantaged*. New York: The American Cancer Society.
- Armstrong, B., and R. Doll. 1975. "Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices." *Int J Cancer* 15:617-631.
- Austin, H., and P. Cole. 1986. "Cigarette smoking and leukemia." *J Chronic Dis* 39:417-421.
- Begg, C. B., A. M. Walker, B. Wessen, and M. Zelen. 1983. "Alcohol consumption and breast cancer" (letter). *Lancet* 1:293-294.
- Beaglehole, R., M. A. Foulkes, I. A. M. Prior et al. 1980. "Cholesterol and mortality in New Zealand Maoris." *Br Med J* 1:285-287.
- Block, G. 1982. "A review of validations of dietary assessment methods." *Am J Epidemiol* 115:492-505.
- Braitman, L. E., E. V. Adlin, and J. L. Stanton, Jr. 1985. "Obesity and caloric intake: The National Health and Nutrition Examination Survey of 1971-1975 (HANES I)." *J Chronic Dis* 38:727-732.
- Brinton, L. A., and J. F. Fraumeni, Jr. 1986. "Epidemiology of uterine cervical cancer." *J Chronic Dis* 39:1051-1065.
- Byers, T., and D. P. Funch. 1982. "Alcohol and breast cancer" (letter). *Lancet* 1:799-800.
- Cambien, F., P. Ducimitiere, and J. Richard. 1980. "Total serum cholesterol and cancer mortality in a middle-aged population." *Am J Epidemiol* 112:388-394.
- Carroll, K. K. 1980. "Lipids and carcinogenesis." *J Environ Pathol Toxicol* 3:253-271.

- Carroll, K. K., and H. T. Khor. 1970. "Effects of dietary fat and dose level of 7,12-dimethylbenz(a)anthracene on mammary tumor incidence in rats." *Cancer Res* 30:2226-2264.
- Carroll, K. K., and H. T. Khor. 1975. "Dietary fat in relation to tumorigenesis." *Prog Biochem Pharmacol* 10:308-353.
- Cox, D. R., and D. Oakes. 1984. *Analysis of Survival Data*. London: Chapman and Hall.
- Day, N. E. 1975. "Some aspects of the epidemiology of esophageal cancer." *Cancer Res* 35:3304-3307.
- Devesa, S. S., and E. L. Diamond. 1983. "Socioeconomic and racial differences in lung cancer incidence." *Am J Epidemiol* 118:818-831.
- Drasar, B. S., and D. Irving. 1973. "Environmental factors and cancer of the colon and breast." *Br J Cancer* 27:167-172.
- Dyer, A. R., J. Stamler, O. Paul et al. 1981. "Serum cholesterol and risk of death from cancer and other causes in three Chicago epidemiological studies." *J Chronic Dis* 34:249-260.
- Eavenson, D., O. T. Grier, J. G. Cision, and R. F. Witter. 1966. "A semiautomated procedure for the determination of serum cholesterol using the Abell-Kendall method." *J Am Oil Chem Soc* 43:652-656.
- Enig, M. G., R. J. Munn, and M. Keeney. 1978. "Dietary fat and cancer trends—a critique." *Fed Proc* 37:2215-2220.
- Feinleib, M. 1981. "On a possible inverse relationship between serum cholesterol and cancer mortality." *Am J Epidemiol* 114:5-10.
- Fleiss, J. L. 1981. *Statistical Methods for Rates and Proportions*. New York: Wiley.
- Freudenheim, J. L., N. E. Johnson, and R. L. Wardrop. 1987. "Misclassification of nutrient intake of individuals and groups using one-, two-, three-, and seven-day food records." *Am J Epidemiol* 126:703-713.
- Garcia-Palmieri, M. R., P. D. Sorlie, R. Costas et al. 1981. "An apparent inverse relationship between serum cholesterol and cancer mortality in Puerto Rico." *Am J Epidemiol* 114:29-40.
- Gaskill, S. P., W. L. McGuire, C. K. Osborne et al. 1979. "Breast cancer mortality and diet in the United States." *Cancer Res* 39:3628-3637.
- Graham, S., J. Marshall, C. Mettlin et al. 1982. "Diet in the epidemiology of breast cancer." *Am J Epidemiol* 116:68-75.
- Gray, G. E., M. C. Pike, and B. E. Henderson. 1979. "Breast cancer incidence and mortality rates in different countries in relation to known risk factors and dietary practices." *Br J Cancer* 39:1-7.
- Greenland, S., and J. M. Robins. 1985. "Confounding and misclassification." *Am J Epidemiol* 122:495-506.
- Haenszel, W., and P. Correa. 1975. "Developments in the epidemiology of stomach cancer over the past decade." *Cancer Res* 35:3452-3459.
- Harvey, E. B., C. Schairer, L. A. Brinton, R. N. Hoover, and J. F. Fraumeni, Jr. 1987. "Alcohol consumption and breast cancer." *Natl Cancer Inst* 78:657-661.
- Hiatt, R. A., and R. O. Bawol. 1984. "Alcoholic beverage consumption and breast cancer incidence." *Am J Epidemiol* 120:676-683.
- Hiatt, R. A., and B. H. Fireman. 1986. "Serum cholesterol and the incidence of cancer in a large cohort." *J Chronic Dis* 39:861-870.
- Hiatt, R. A., G. D. Friedman, R. D. Bawol et al. 1982. "Breast cancer and serum cholesterol." *JNCI* 68:885-889.

- Hiatt, R. A., A. Klatsky, and M. A. 1982. "Breast cancer in a prepaid health plan." *Am J Epidemiol* 115:1-10.
- Hirayama, T. 1978. "Epidemiology of cancer in Japan." *Prev Med* 7:173-195.
- Hirohata, T., T. Shigematsu, A. M. 1982. "Relation to diet and reproduction." *Natl Cancer Inst Monogr* 69:1-10.
- Hislop, T. G., A. J. Coldman, J. M. 1982. "Patterns and risk of breast cancer." *Br J Cancer* 45:1-10.
- Ingram, D. M. 1981. "Trends in diet and cancer." *Nutr Cancer* 3:1-10.
- International Collaborative Group. 1982. "Diet and cancer in men aged 40-59." *JAMA* 248:2853-2858.
- Jones, D. Y., A. Schatzkin, S. B. G. 1982. "National Health and Nutrition Survey." *J Natl Cancer Inst* 79:1-10.
- Kagan, A., D. L. McGee, K. Yano. 1982. "Diet and cancer in a Japanese-American population." *Am J Epidemiol* 114:11-20.
- Kark, J. D., A. H. Smith, and C. G. F. 1982. "The incidence of cancer in Evansville, Indiana." *Am J Epidemiol* 115:1-10.
- Katsouyanni, K., D. Trichopoulos, P. 1982. "Control study in Greece." *Int J Epidemiol* 11:1-10.
- Kelsey, J. L. 1979. "A review of the epidemiology of cancer." *Epidemiol Rev* 1:74-109.
- Keys, A., C. Aravanis, H. Blackburn et al. 1982. "The Seven Countries Study." *Am J Epidemiol* 115:1-10.
- Kinlen, L. J. 1982. "Meat and fat consumption and cancer in religious orders in Britain." *Lancet* i:10-15.
- Kitagawa, E. M., and P. M. Hauser. 1982. "Diet and cancer in Japan." *Am J Epidemiol* 115:1-10.
- Kozarevic, D. J., D. McGee, N. Vojvoda. 1982. "Yugoslavia Cardiovascular Disease Study." *Am J Epidemiol* 115:1-10.
- Kritchevsky, D., M. M. Weber, C. L. 1982. "Diet and cancer in men." *Am J Epidemiol* 115:1-10.
- Kritchevsky, D., M. M. Weber, and C. L. 1982. "Content in initiation and promotion of tumorigenesis in rats." *Cancer Res* 42:1-10.
- La Vecchia, C., A. Decarli, S. Franceschi. 1982. "Breast cancer in women." *JNCI* 72:1-10.
- Le, M. G., C. Hill, A. Kramer, and F. 1982. "Diet and breast cancer in a French population." *Am J Epidemiol* 115:1-10.
- Le, M. G., L. H. Moulton, C. Hill, and A. 1982. "Diet and alcohol in a case-control study of breast cancer." *Am J Epidemiol* 115:1-10.
- Lea, A. J. 1965. "New observations on the incidence of cancer in European countries." *Br Med J* 1:1-10.
- Logan, W. P. 1982. *Cancer mortality in the United States*. New York: National Cancer Institute.

- Hiatt, R. A., A. Klatsky, and M. A. Armstrong. 1988. "Alcohol consumption and the risk of breast cancer in a prepaid health plan." *Cancer Res* 48:2284-2287.
- Hirayama, T. 1978. "Epidemiology of breast cancer with special reference to the role of diet." *Prev Med* 7:173-195.
- Hirohata, T., T. Shigematsu, A. M. Nomura et al. 1985. "Occurrence of breast cancer in relation to diet and reproductive history: A case-control study in Fukuoka, Japan." *Natl Cancer Inst Monogr* 69:187-190.
- Hislop, T. G., A. J. Coldman, J. M. Elwood et al. 1986. "Childhood and recent eating patterns and risk of breast cancer." *Cancer Detect Prev* 9:47-58.
- Ingram, D. M. 1981. "Trends in diet and breast cancer mortality in England and Wales 1928-1977." *Nutr Cancer* 3:75-80.
- International Collaborative Group. 1982. "Circulating cholesterol level and risk of death from cancer in men aged 40-69 years: experience of an international collaborative group." *JAMA* 248:2853-2859.
- Jones, D. Y., A. Schatzkin, S. B. Green et al. 1987. "Dietary fat and breast cancer in the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study." *J Natl Cancer Inst* 79:465-471.
- Kagan, A., D. L. McGee, K. Yano et al. 1981. "Serum cholesterol and mortality in a Japanese-American population: The Honolulu Heart Program." *Am J Epidemiol* 114:11-20.
- Kark, J. D., A. H. Smith, and C. G. Hames. 1980. "The relationship of serum cholesterol to the incidence of cancer in Evans County, Georgia." *J Chronic Dis* 33:311-322.
- Katsouyanni, K., D. Trichopoulos, P. Boyle et al. 1986. "Diet and breast cancer: A case-control study in Greece." *Int J Cancer* 38:815-820.
- Kelsey, J. L. 1979. "A review of the epidemiology of human breast cancer." *Epidemiol Rev* 1:74-109.
- Keys, A., C. Aravanis, H. Blackburn et al. 1985. "Serum cholesterol and cancer mortality in the Seven Countries Study." *Am J Epidemiol* 121:870-883.
- Kinlen, L. J. 1982. "Meat and fat consumption and cancer mortality: A study of strict religious orders in Britain." *Lancet* 1:946-949.
- Kitagawa, E. M., and P. M. Hauser. 1973. *Differential Mortality in the United States: A Study in Socioeconomic Epidemiology*. Cambridge, MA: Harvard University Press.
- Kozarevic, D. J., D. McGee, N. Vojvodic et al. 1981. "Serum cholesterol and mortality: The Yugoslavia Cardiovascular Disease Study." *Am J Epidemiol* 114:21-28.
- Kritchevsky, D., M. M. Weber, C. L. Buck et al. 1986. "Calories, fat and cancer." *Lipids* 21:272-274.
- Kritchevsky, D., M. M. Weber, and D. M. Klurfeld. 1984. "Dietary fat versus caloric content in initiation and promotion of 7,12-dimethylbenz(a)anthracene-induced mammary tumorigenesis in rats." *Cancer Res* 44:3174-3177.
- La Vecchia, C., A. Decarli, S. Franceschi et al. 1985. "Alcohol consumption and the risk of breast cancer in women." *JNCI* 75:61-65.
- Le, M. G., C. Hill, A. Kramer, and R. Flamant. 1984. "Alcoholic beverage consumption and breast cancer in a French case-control study." *Am J Epidemiol* 120:350-357.
- Le, M. G., L. H. Moulton, C. Hill, and A. Kramer. 1986. "Consumption of dairy produce and alcohol in a case-control study of breast cancer." *JNCI* 77:633-636.
- Lea, A. J. 1965. "New observations on distribution of neoplasms of female breast in certain European countries." *Br Med J* 1:488-490.
- Logan, W. P. 1982. *Cancer mortality by occupation and social class 1851-1971*. London:

- Her Majesty's Stationary Office (Studies on Medical and Population Subjects No. 44) (also IARC Scientific Publication No. 36).
- Lubin, J. H., P. E. Burns, W. J. Blot et al. 1981. "Dietary factors and breast cancer risk." *Int J Cancer* 28:685-689.
- Lubin, F., Y. Wax, and B. Modan. 1986. "Role of fat, animal protein, and dietary fiber in breast cancer etiology: A case-control study." *JNCI* 77:605-612.
- Luft, H. S. 1978. *Poverty and Health*. Cambridge, MA: Ballinger.
- Mandel, J. S., and L. M. Schuman. 1979. "Epidemiology of cancer of the prostate." *Epidemiol Rev* 1:1-73.
- McMichael, A. J., O. M. Jensen, D. M. Parkin, and D. G. Zaridze. 1984. "Dietary and endogenous cholesterol and human cancer." *Epidemiol Rev* 6:192-216.
- Miller, A. B., A. Kelly, N. W. Choi et al. 1978. "A study of diet and breast cancer." *Am J Epidemiol* 107:499-509.
- Morris, D. L., N. O. Borhani, E. Fitzsimons et al. 1983. "Serum cholesterol and cancer in the Hypertension Detection and Follow-up Program." *Cancer* 52:1754-1759.
- Muller, H. G. 1930. "The cholesterol metabolism in health and anemia." *Medicine* 9:119-174.
- National Center for Health Statistics. 1972. *Instruction Manual. Data Collection. Part 15a*. NHANES Examination Staff Procedures Manual for the Health and Nutrition Examination Survey, 1971-1973. Washington, DC: U.S. Government Printing Office 722-554/89.
- National Center for Health Statistics. 1980. Serum cholesterol levels by persons 4-74 years of age by socioeconomic characteristics. *Vital and Health Statistics*. Series 11, No. 217. DHEW Pub. No. (PHS) 80-1667. Washington, DC: U.S. Government Printing Office.
- Nomura, A. M., T. Hirohata, L. N. Kolonel et al. 1985. "Breast cancer in Caucasian and Japanese women in Hawaii." *Natl Cancer Inst Monogr* 69:191-196.
- O'Connell, D. L., B. S. Hulka, L. E. Chambless et al. 1987. "Cigarette smoking, alcohol consumption, and breast cancer risk." *JNCI* 78:229-234.
- Paganini-Hill, A., and R. K. Ross. 1983. "Breast cancer and alcohol consumption." *Lancet* 2:626-627.
- Peterson, B., and E. Trell. 1983. "Premature mortality in middle-aged men: Serum cholesterol as risk factor." *Klin Wochenschr* 63:795-801.
- Phillips, R. L. 1975. "Role of life-style and dietary habits in risk of cancer among Seventh-Day Adventists." *Cancer Res* 35:3513-3522.
- Phillips, R. L., and D. A. Snowdon. 1983. "Association of meat and coffee use with cancers of the large bowel, breast, and prostate among Seventh-Day Adventists: Preliminary results." *Cancer Res* 43(suppl 5):2403a-2408s.
- Rose, G., H. Blackburn, A. Keys et al. 1974. "Colon cancer and blood cholesterol." *Lancet* 1:181-183.
- Rose, G., and M. J. Shipley. 1980. "Plasma lipids and mortality, a source of error." *Lancet* 1:523-526.
- Rosenberg, L., D. Stone, S. Shapiro et al. 1982. "Breast cancer and alcoholic-beverage consumption." *Lancet* 1:267-271.
- Rosner, B., W. C. Willett, and D. Spiegelman. In press. "Correction of logistic regression relative risk estimates and confidence intervals for systematic within-person measurement error." *Stat Med*.
- Rothman, K. J. 1986. *Modern Epidemiology*. Boston: Little, Brown.
- Salonen, J. T. 1982. "Risk of cancer and death in relation to serum cholesterol: a longitudinal

- study in an Eastern Fin  
*Epidemiol* 116:622-630
- SAS Institute, Inc. 1983. *SUG*
- Schatzkin, A., R. N. Hoover, serum cholesterol and i  
Follow-up Study." *Canc*
- Schatzkin, A., D. Y. Jones, R cancer in the epidemiolo  
Examination Survey." *A*
- Schatzkin, A., P. R. Taylor, C. NHANES I epidemiology
- Schottenfeld, D., and S. J. Wi  
*Prevention*. D. Schotten  
ders Company, pp. 703-
- Sherwin, R. W., D. N. Wentwo  
cancer mortality in 361,  
Trial." *JAMA* 257:943-
- Sondik, E. J., J. L. Young, J. *Statistics Review*. DHH  
tional Cancer Institute,
- Sorlie, P. D., and M. Feinlei  
analysis of time trends i
- Stemmerman, G. N., A. Nomu  
cancer incidence in Hav
- Talamini, R., C. La Vecchia, A. a northern Italian popul
- Tannenbaum, A. 1942. "The g  
*Cancer Res* 2:468-475.
- Thomas, C. B., K. R. Duszyn  
adulthood and subsequer  
94.
- Tornberg, S. A., L. E. Holm, J. the colon and rectum in  
*J Med* 315:1629-1633.
- Vitols, S., M. Bjorkkolm, G. ( malignancy due to eleva  
Evidence from studies i
- Wallace, R. B., C. Rost, L. J relationship to plasma  
918.
- Watt, B. K., and A. L. Merril  
*Agriculture Handbook*. 8  
ture.
- Webster, L. A., P. M. Layde, I breast cancer." *Lancet* 2
- Westlund, K., and Nicolaysen, cholesterol." *Scand J C*
- Willett, W. C., G. A. Colditz, intake and risk of breast

- study in an Eastern Finnish population with high overall cholesterol level." *Am J Epidemiol* 116:622-630.
- SAS Institute, Inc. 1983. *SUGI Supplemental Library User's Guide*, 1983. Cary, NC.
- Schatzkin, A., R. N. Hoover, P. R. Taylor et al. 1988. "A site-specific analysis of total serum cholesterol and incident cancer results from the NHANES I Epidemiologic Follow-up Study." *Cancer Res* 48:452-458.
- Schatzkin, A., D. Y. Jones, R. N. Hoover et al. 1987. "Alcohol consumption and breast cancer in the epidemiologic follow-up study of the first National Health and Nutrition Examination Survey." *N Engl J Med* 316:1169-1173.
- Schatzkin, A., P. R. Taylor, C. L. Carter et al. 1987. "Serum cholesterol and cancer in the NHANES I epidemiologic follow-up study." *Lancet* 2:298-301.
- Schottenfeld, D., and S. J. Winawar. 1982. Large intestine. In *Cancer Epidemiology and Prevention*. D. Schottenfeld and J. F. Fraumeni, Jr., eds. Philadelphia: W. B. Saunders Company, pp. 703-727.
- Sherwin, R. W., D. N. Wentworth, J. A. Cutler et al. 1987. "Serum cholesterol levels and cancer mortality in 361,662 men screened for the Multiple Risk Factor Intervention Trial." *JAMA* 257:943-948.
- Sondik, E. J., J. L. Young, J. W. Horm, and L. A. G. Riles. 1986. *1986 Annual Cancer Statistics Review*. DHHS, Public Health Service, National Institutes of Health, National Cancer Institute, Bethesda, MD.
- Sorlie, P. D., and M. Feinleib. 1982. "The serum cholesterol-cancer relationship: An analysis of time trends in the Framingham Study." *JNCI* 69:989-996.
- Stemmerman, G. N., A. Nomura, L. K. Heilbrun et al. 1981. "Serum cholesterol and colon cancer incidence in Hawaiian Japanese men." *JNCI* 67:1179-1182.
- Talamini, R., C. La Vecchia, A. Decarli et al. 1984. "Social factors, diet and breast cancer in a northern Italian population." *Br J Cancer* 49:723-729.
- Tannenbaum, A. 1942. "The genesis and growth of tumors. III. Effects of high-fat diet." *Cancer Res* 2:468-475.
- Thomas, C. B., K. R. Duszynski, and J. W. Schaffer. 1982. "Cholesterol levels in young adulthood and subsequent cancer: A preliminary note." *Johns Hopkins Med J* 150:89-94.
- Tornberg, S. A., L. E. Holm, J. M. Carstensen, and G. A. Eklund. 1986. "Risks of cancer of the colon and rectum in relation to serum cholesterol and beta-lipoprotein." *New Engl J Med* 315:1629-1633.
- Vitols, S., M. Bjorkkolm, G. Gahrton, and C. Peterson. 1985. "Hypocholesterolaemia in malignancy due to elevated low-density-lipoprotein-receptor activity in tumour cells: Evidence from studies in patients with leukemia." *Lancet* 2:1150-1154.
- Wallace, R. B., C. Rost, L. F. Burmeister et al. 1982. "Cancer incidence in humans: relationship to plasma lipids and relative weight." *J Natl Cancer Inst* 68:915-918.
- Watt, B. K., and A. L. Merrill. 1963. *Composition of Foods: Raw, Processed, Prepared. Agriculture Handbook*. 8th ed. (rev.). Washington, DC: U.S. Department of Agriculture.
- Webster, L. A., P. M. Layde, P. A. Wingo et al. 1983. "Alcohol consumption and risk of breast cancer." *Lancet* 2:724-726.
- Westlund, K., and Nicolaysen, R. 1972. "Ten-year mortality and morbidity related to serum cholesterol." *Scand J Clin Lab Invest* 30(suppl 127):3-24.
- Willett, W. C., G. A. Colditz, M. J. Stampfer et al. 1986. "A prospective study of alcohol intake and risk of breast cancer (abstract)." *Am J Epidemiol* 124:540-541.

- Willett, W. C., M. J. Stampfer, G. A. Colditz et al. 1987. "Dietary fat and the risk of breast cancer." *N Engl J Med* 316:22-28.
- Williams, R. R., and J. W. Horm. 1977. "Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: Interview study from the Third National Cancer Survey." *J Natl Cancer Inst* 58:525-547.
- Williams, R. R., P. D. Sorlie, M. Feinleib et al. 1981. "Cancer incidence by levels of cholesterol." *JAMA* 245:247-252.
- Wingard, D. L., M. H. Criqui, M. J. Holdbrook, and E. Barrett-Connor. 1984. "Plasma cholesterol and cancer morbidity and mortality in an adult community." *J Chronic Dis* 37:401-406.
- Wynder, E. L., I. J. Bross, and T. Hirayama. 1960. "A study of the epidemiology of cancer of the breast." *Cancer* 13:559-601.
- Wynder, E. L., and D. Hoffman. 1982. Tobacco. In *Cancer Epidemiology and Prevention*. D. Schottenfeld and J. F. Fraumeni, J., eds. Philadelphia: W. B. Saunders Company, pp. 277-292.
- Yaari, S., U. Goldbourt, S. Evan-Zohar et al. 1981. "Associations of serum high density lipoprotein and total cholesterol with total, cardiovascular, and cancer mortality in a 7-year prospective study of 10,000 men." *Lancet* 1:1011-1014.

## 6

## Cerebrovas

LON R. WHITE, K.  
AND PHILIP A. W.

In most developed  
rologic cause of mo  
dramatic manifestat  
strophic event whos  
vascular disease pro  
failure of perfusion  
chain may be precip  
that alter local lamin  
at the site of a disr  
development of the u  
of decades, wherea  
likely to express th  
prevention of stroke  
of the total pathogen  
of the underlying v  
cipitous event.

Although we l  
vascular process lea  
ting at the time of t  
standing of the patho  
scored by certain pa  
although both obesit  
as predictors of hear  
for stroke in most s  
death in Japan for m  
in recent years the  
important and heart  
the United States (T  
Over the past